The polyglandular doctrine which was introduced by Eppinger, Falta and Rudinger in 1908 has been generally accepted.

And many problems on pathological metabolism, especially diabetes mellitus have been tried to be explained on this principle. In their opinion, diabetes comes of the disturbance of the balance between the pancreas and adrenals. It was made clear by the famous discovery by Mering and Minkowski that the pancreas provides the organism with something essentials for the metabolism of carbohydrates. But as until recently, as the history of the isolation of the active hormon of the pancreas has been that of failure, any special evidence of an antagonism between the pancreas and the adrenals is still lacking.

In 1920 our director, Prof. Kumagai who had been engaged in researches in the function of the pancreas many years, succeeded in isolating of a certain substance, which was capable of raising the sugar consumption of the isolated surviving heart perfused with Locke's solution, from the pancreas and reported the results at the Meeting of Internal Medicine in Japan in 1921. In April 1922, he and Sato reported all about it and the method of its preparation which had made steady progress and had been greatly simplified since then, and the therapeutic effect of the extract upon diabetic patients.

Being favoured with the extract by the kindness of Prof. Kumagai, I employed myself in the experiment to determine definitely whether there was any antagonism between this pancreatic hormon and the adrenalin.
Before the main experiments were begun the hypoglycemic effect in normal rabbits was examined, to see to what extent the extract of pancreas had influence on adrenalin and other experimental hyperglycemia. The rabbits employed in this investigation were selected as uniform as possible in nutritive condition and size. The blood specimens were taken from ear veins and the blood sugar was estimated by Bang's new method. At the end of the observations whenever possible the glycogen in liver and muscle was determined by Pflüger's method, and the sugar solution which was produced by hydrolyzing the glycogen, was estimated by Momose's modification of Kumagawa-Suto's method.

(1) THE EFFECT OF THE PANCREATIC EXTRACT ON THE NORMAL RABBITS.

To what degree our pancreatic extract when injected by itself, caused the fall of the sugar content in the blood of normal rabbits was observed in the following experiments.

In each experiment, first a sample of normal blood was taken, and then an extract of pancreas was injected subcutaneously. After that further samples of blood were taken at regular intervals.

As the same sort of results were obtained from almost all the rabbits, a few cases are thought enough to be stated as examples (Experiment I, II and III.)

**Experiment I.**

Rabbit 1. Wt. 1.38 kilos.

The blood sugar before injection 0.118 per cent.

At 9h30' a.m. 1 c.c. of pancreatic extract subcutaneously injected.

10h00' blood sugar 0.093 per cent.

10h30' blood sugar 0.075 per cent.

11h00' blood sugar 0.060 per cent.

11h30' blood sugar 0.048 per cent.

At this period, the rabbit is lying on its side and is so hyperexcitable and fearful that even the slightest stimulus can cause the animal to run wildly about. Its respiration is rapid and dyspnoic.

Spontaneously or by the mechanical stimulation of skin, a fit of convulsions sets in during which the rabbit throws itself and rolls over sideways with its head bent back, and when the convulsions are over, the rabbit becomes comatose. After an interval of over ten minutes, the animal is attacked with convulsions again.

12h30', animal is moribund and blood sample is taken from the heart. Blood sugar content 0.024 per cent.

Liver showed a glycogen content of 0.43 per cent.
In the following two examples, the blood sugar and the rectal temperature were determined after the subcutaneous injection of the pancreatic extract.

**Experiment II.**

Rabbit 2. Wt. 1.3 kilos.

At 10h55' a.m. The blood sugar before injection 0.109 per cent, rectal temperature 38.4°C.

11h00' 1 c.c. of pancreatic extract subcutaneously injected.

11h30' blood sugar 0.088 per cent.

12h00' blood sugar 0.054 per cent, rectal temperature 37.8°C. Animal becomes weak and can not stand and walk.

1p00' blood sugar 0.031 per cent. Convulsions occurred. Rectal temperature 37.0°C.

2h00' blood sugar 0.020 per cent, rectal temperature 37.0°C, under convulsion and coma died.

The glycogen content in the liver showed 0.30 per cent.

**Experiment III.**

Rabbit 3. Wt. 1.18 kilos.

At 9h15' a.m. Blood sugar before injection 0.083 per cent, rectal temperature 38.2°C.

9h50' blood sugar 0.078 per cent, rectal temperature 38.2°C.

10h20' blood sugar 0.078 per cent, rectal temperature 38.2°C.

10h50' blood sugar 0.062 per cent, rectal temperature 38.0°C.

11h50' blood sugar 0.047 per cent, animal becomes excitable and weak, rectal temperature 37.8°C.

12h50' blood sugar 0.043 per cent, rectal temperature 37.8°C, convolution.

1h50' blood sugar 0.040 per cent, rectal temperature 37.0°C, collapse and death.

Liver showed a glycogen content of 0.67 per cent.

Muscle showed a glycogen content of 0.32 per cent.

These three results are given in curve form in Figure 1.
Our pancreatic extract causes the rapid fall of blood sugar in normal rabbits within 2–3 hours. And in the majority of cases the blood sugar decreases to its minimum, arriving at its minimum about 3 hours after the subcutaneous injection and when the height of blood sugar is about 0.045 per cent, the peculiar symptoms, especially convulsions, show themselves.

The rectal temperature does not fall at the same rate as the blood sugar, but falls rapidly only when the animal collapses.

The results of the experiments with insulin by Banting and others agree in all particulars with those of mine.

(2) **THE DIFFERENCE OF HYPOGLYCEMIC EFFECTS IN RABBITS INJECTED WITH PANCREATIC EXTRACT SUBCUTANEOUSLY AND INTRAVENOUSLY.**

Each pair of rabbits used in this comparative investigation were as uniform as possible in weight and nutritional condition. And the rabbits had been kept fasting 24 hours before the experiment.

**Experiment IV.**

Subcutaneous and intravenous injection of 1 c.c. pancreatic extract.

<table>
<thead>
<tr>
<th>Time of taking blood</th>
<th>Rabbit 4, 1.7 kilos. (Subcutaneous injection)</th>
<th>Rabbit 5, 1.7 kilos. (Intravenous injection)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial blood sugar</td>
<td>0.110</td>
<td>0.118</td>
</tr>
<tr>
<td>30' after injection</td>
<td>0.060</td>
<td>0.110</td>
</tr>
<tr>
<td>1 hr. &quot;</td>
<td>0.060</td>
<td>0.094</td>
</tr>
<tr>
<td>2 hrs. &quot;</td>
<td>0.055</td>
<td>0.094</td>
</tr>
<tr>
<td>3 hrs. &quot;</td>
<td>0.058</td>
<td>0.100</td>
</tr>
<tr>
<td>4 hrs. &quot;</td>
<td>0.085</td>
<td>0.106</td>
</tr>
<tr>
<td>5 hrs. &quot;</td>
<td>0.088</td>
<td>0.109</td>
</tr>
</tbody>
</table>

Glycogen determination not made.
Experiment V.

Subcutaneous and intravenous injection of 1 c.c. pancreatic extract.

<table>
<thead>
<tr>
<th>Time of taking blood</th>
<th>Rabbit 6a 1.8 kilos. (Subcutaneous injection)</th>
<th>Rabbit 6b 1.8 kilos. (Intravenous injection)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial blood sugar</td>
<td>0.083</td>
<td>0.096</td>
</tr>
<tr>
<td>30' after injection</td>
<td>0.071</td>
<td>0.073</td>
</tr>
<tr>
<td>1 hr. &quot; &quot;</td>
<td>0.056</td>
<td>0.060</td>
</tr>
<tr>
<td>2 hrs. &quot; &quot;</td>
<td>0.052</td>
<td>0.068</td>
</tr>
<tr>
<td>3 hrs. &quot; &quot;</td>
<td>0.070</td>
<td>0.060</td>
</tr>
<tr>
<td>4 hrs. &quot; &quot;</td>
<td>0.073</td>
<td>0.058</td>
</tr>
<tr>
<td>5 hrs. &quot; &quot;</td>
<td>0.078</td>
<td>0.061</td>
</tr>
</tbody>
</table>

Rabbit 6 a......Glycogen content in the liver showed 0.73 per cent.
Rabbit 6 b......Glycogen content in the liver showed 0.87 per cent.

Experiment VI.

Subcutaneous and intravenous injection of 1 c.c. pancreatic extract.

<table>
<thead>
<tr>
<th>Time of taking blood</th>
<th>Rabbit 7. 1.6 kilos. (Subcutaneous injection)</th>
<th>Rabbit 8. 1.6 kilos. (Intravenous injection)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial blood sugar</td>
<td>0.109</td>
<td>0.102</td>
</tr>
<tr>
<td>30' after injection</td>
<td>0.088</td>
<td>0.061</td>
</tr>
<tr>
<td>1 hr. &quot; &quot;</td>
<td>0.054</td>
<td>0.064</td>
</tr>
<tr>
<td>2 hrs. &quot; &quot;</td>
<td>0.031 convulsions</td>
<td>0.065</td>
</tr>
<tr>
<td>3 hrs. &quot; &quot;</td>
<td>0.030 death</td>
<td>0.053</td>
</tr>
<tr>
<td>4 hrs. &quot; &quot;</td>
<td></td>
<td>0.076</td>
</tr>
<tr>
<td>5 hrs. &quot; &quot;</td>
<td></td>
<td>0.081</td>
</tr>
</tbody>
</table>

Rabbit 7......Glycogen content in the liver showed 0.12 per cent.
Rabbit 8......Glycogen estimation not made.
Experiment VII.

Subcutaneous and intravenous injection of 1 c.c. pancreatic extract.

<table>
<thead>
<tr>
<th>Time of taking blood</th>
<th>Rabbit 9. 1.9 kilos. (Subcutaneous injection)</th>
<th>Rabbit 10. 1.8 kilos. (Intravenous injection)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blood sugar (per cent)</td>
<td></td>
</tr>
<tr>
<td>Initial blood sugar</td>
<td>0.110</td>
<td>0.113</td>
</tr>
<tr>
<td>30' after injection</td>
<td>0.103</td>
<td>0.072</td>
</tr>
<tr>
<td>1 hr. &quot; &quot;</td>
<td>0.086</td>
<td>0.070</td>
</tr>
<tr>
<td>2 hrs. &quot; &quot;</td>
<td>0.064</td>
<td>0.110</td>
</tr>
<tr>
<td>3 hrs. &quot; &quot;</td>
<td>0.053</td>
<td>0.100</td>
</tr>
<tr>
<td>4 hrs. &quot; &quot;</td>
<td>0.060</td>
<td>0.108</td>
</tr>
<tr>
<td>5 hrs. &quot; &quot;</td>
<td>0.060</td>
<td>0.101</td>
</tr>
</tbody>
</table>

Rabbit 9......Glycogen content in the liver 0.43 per cent.
Rabbit 10......Glycogen content in the liver 0.66 per cent.

Experiment VIII.

Subcutaneous and intravenous injection of 1 c.c. pancreatic extract.

<table>
<thead>
<tr>
<th>Time of taking blood</th>
<th>Rabbit 11. 2.0 kilos. (Subcutaneous Injection)</th>
<th>Rabbit 12. 1.9 kilos. (Intravenous injection)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blood sugar (per cent)</td>
<td></td>
</tr>
<tr>
<td>Initial blood sugar</td>
<td>0.085</td>
<td>0.094</td>
</tr>
<tr>
<td>30' after injection</td>
<td>0.040</td>
<td>0.043 convulsions</td>
</tr>
<tr>
<td>1 hr. &quot; &quot;</td>
<td>0.040</td>
<td>0.038</td>
</tr>
<tr>
<td>2 hrs. &quot; &quot;</td>
<td>0.034 convulsions</td>
<td>0.033 death</td>
</tr>
<tr>
<td>3 hrs. &quot; &quot;</td>
<td>0.030 death</td>
<td></td>
</tr>
<tr>
<td>4 hrs. &quot; &quot;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 hrs. &quot; &quot;</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Rabbit 11......Glycogen content in the liver showed 0 per cent.
Rabbit 12......Glycogen content in the liver showed 0.09 per cent.
Experiment IX.

<table>
<thead>
<tr>
<th>Time of taking blood</th>
<th>Rabbit 13. 1.9 kilos. (Subcutaneous injection)</th>
<th>Rabbit 14. * 2.0 kilos. (Fractional intravenous injection)</th>
<th>Rabbit 15. 1.9 kilos. (Intravenous injection)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial blood sugar</td>
<td>0.108</td>
<td>0.110</td>
<td>0.114</td>
</tr>
<tr>
<td>30' after injection</td>
<td>0.069</td>
<td>0.082</td>
<td>0.085</td>
</tr>
<tr>
<td>1 hr. &quot; &quot;</td>
<td>0.044</td>
<td>0.060</td>
<td>0.057</td>
</tr>
<tr>
<td>2 hrs. &quot; &quot;</td>
<td>0.036 convulsions</td>
<td>0.051</td>
<td>0.060</td>
</tr>
<tr>
<td>3 hrs. &quot; &quot;</td>
<td>0.030</td>
<td>0.044</td>
<td>0.090</td>
</tr>
<tr>
<td>4 hrs. &quot; &quot;</td>
<td>0.025 death</td>
<td>0.046</td>
<td>0.092</td>
</tr>
<tr>
<td>5 hrs. &quot; &quot;</td>
<td></td>
<td>0.044</td>
<td>0.090</td>
</tr>
</tbody>
</table>

* The same dose of extract was divided into four portions and injected within one hour at intervals of 25 minutes.

Rabbit 13......Glycogen content in the liver showed 0.163 per cent.
Rabbit 14......Glycogen content in the liver showed 0.103 per cent.
Rabbit 15......Glycogen content in the liver showed 0.77 per cent.

Experiment X.

<table>
<thead>
<tr>
<th>Time of taking blood</th>
<th>Rabbit 16. 1.8 kilos. (Subcutaneous injection)</th>
<th>Rabbit 17. * 1.8 kilos. (Fractional intravenous injection)</th>
<th>Rabbit 18. 1.8 kilos. (Intravenous injection)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial blood sugar</td>
<td>0.110</td>
<td>0.108</td>
<td>0.103</td>
</tr>
<tr>
<td>30' after injection</td>
<td>0.089</td>
<td>0.072</td>
<td>0.078</td>
</tr>
<tr>
<td>1 hr. &quot; &quot;</td>
<td>0.062</td>
<td>0.051</td>
<td>0.056</td>
</tr>
<tr>
<td>2 hrs. &quot; &quot;</td>
<td>0.042 convulsions</td>
<td>0.040 convulsions</td>
<td>0.051</td>
</tr>
<tr>
<td>3 hrs. &quot; &quot;</td>
<td>0.025</td>
<td>0.038</td>
<td>0.079</td>
</tr>
<tr>
<td>4 hrs. &quot; &quot;</td>
<td>0.020</td>
<td></td>
<td>0.080</td>
</tr>
<tr>
<td>5 hrs. &quot; &quot;</td>
<td>0.020</td>
<td></td>
<td>0.095</td>
</tr>
</tbody>
</table>

* The same dose of extract was divided into four portions and injected within one hour at intervals of 25 minutes.

The results of the experiments from IV. to X. are also given in curve forms (from Fig. 2 to 8).
Generally the reduction of blood sugar and hypoglycemic symptom of far higher degree resulted from the subcutaneous injection than the intravenous one. This result does not consist with that of McCormick and others.

This difference decreased according as the extract was purified, and yet the subcutaneous injection of even the most purified pancreatic extract produced about twice as much blood sugar fall as the intravenous injection.

It follows from this result that the most suitable method of the application of the extract is the subcutaneous injection. The effect of the fractional intravenous injection closely resembles that of subcutaneous injection.

A similar difference in the mode of the glycosuric action is observed between the subcutaneous and intravenous application of adrenalin, as it was first proved by Loewi.\(^8\)

Pollak\(^6\) confirmed that the subcutaneous injection of adrenalin is accompanied by higher hyperglycemia than the intravenous administration.
Ritzmann\textsuperscript{10} produced the adrenalin glycosuria most easily through the continuous intravenous injection of adrenalin, a fact, which is explained as due to the rapid oxidation of adrenalin introduced at once time into the blood stream.

Others believed that the cause of the weaker effect during the course of intravenous injection would be seekd in the unfavourable conditions of the circulation of the liver, which is brought about by the contraction of the blood-vessels and thus its effect fails to appear on account of the slower resorption.

The pancreas hormone, which is at one time introduced intravenously, is rapidly destroyed and remains without effect or excreted, so that it can not unfold its effect corresponding to the quantity applied, while on the other hand the subcutaneous injection of the pancreas hormone is gradually absorbed and produced a strong action, which corresponds to the effect, as in the case with the continuous injection of the pancreas hormone intravenously in small dosis.

Fig. 4. (Exp. VI.) Curves of blood sugar following injection of extracts subcutaneously and intravenously.

Fig. 5. (Exp. VII.) Curves of blood sugar following injection of extracts subcutaneously and intravenously.
Our findings with the pancreas hormone would perhaps be explained in the analogous way, in which the supposed spasm of the blood-vessels is by no means taken into consideration.

Fig. 6. (Exp. VIII.) Curves of blood sugar following injection of extract subcutaneously and intravenously.

Fig. 7. (Exp. IX.) Curves of blood sugar following injection of extracts subcutaneously, intravenously and fractionally-intravenously.

C: Convulsions.
D: Became moribund.
Fig. 8. (Exp. X.). Curves of blood sugar following injection of extracts subcutaneously, intravenously and fractionally intravenously.
C: Convulsions.
D: Moribund.

(3) THE EFFECT OF ADRENALIN ON THE FALL OF BLOOD SUGAR CAUSED BY THE PANCREATIC EXTRACT.

In our Laboratory it was observed that the hypoglycemic symptoms caused in normal rabbits by the active pancreatic extract which had been isolated were removed to some extent by the injection of adrenalin. This very fact aroused me an interest to examine to what extent an antagonism would be produced between the pancreatic extract and adrenalin. In each of the following three experiments 1 c.c. of pancreatic extract was injected, when the hyperglycemia of adrenalin had become evident.
Experiment XI.

Rabbit 19. 1.6 kilos.

Blood sugar before injection 0.100 per cent.
At 9h20' a.m., 1 c.c. of adrenalin subcutaneously injected.
9h50', blood sugar 0.159 per cent.
10h20', blood sugar 0.204 per cent and 1 c.c. of pancreatic extract subcutaneously injected.
10h50', blood sugar 0.180 per cent.
11h20', blood sugar 0.151 per cent.
12h20', blood sugar 0.151 per cent.
12h20', blood sugar 0.032 per cent.
1h20', blood sugar 0.091 per cent.
2h20', blood sugar 0.043 per cent; convulsions.
3h30', blood sugar 0.050 per cent.
4h20', blood sugar 0.065 per cent.

Experiment XII.

Rabbit 20. 1.6 kilos.

Blood sugar before injection 0.090 per cent.
At 9h40' a.m., 1 c.c. of adrenalin subcutaneously injected.
10h10', blood sugar 0.145 per cent.
10h40', blood sugar 0.180 per cent and 1 c.c. of pancreatic extract subcutaneously injected.
11h10', blood sugar 0.192 per cent.
11h40', blood sugar 0.171 per cent.
12h40', blood sugar 0.149 per cent.
1h40', blood sugar 0.161 per cent.
2h40', blood sugar 0.065 per cent.
3h40', blood sugar 0.045 per cent.
4h40', blood sugar 0.050 per cent.

Experiment XIII.

Rabbit 21. 1.6 kilos.

Blood sugar before injection 0.080 per cent.
At 10h00' a.m., 1 c.c. of adrenalin subcutaneously injected.
10h30', blood sugar 0.129 per cent.
11h00', blood sugar 0.161 per cent and 1 c.c. of pancreatic extract subcutaneously injected.
11h30', blood sugar 0.170 per cent.
12h00', blood sugar 0.162 per cent.
12h00', blood sugar 0.102 per cent.
1h00', blood sugar 0.111 per cent.
2h00', blood sugar 0.079 per cent.
3h00', blood sugar 0.066 per cent.
4h00', blood sugar 0.055 per cent.
5h00', blood sugar 0.070 per cent.
The results of experiments from XI to XIII are given in curve form in Figure 9.

Fig. 9. (Exp. XI, XII and XIII) first adrenalin and then pancreatic extract injected. At the first arrow 1 c.c. of adrenalin (1:1000) and at the second arrow 1 c.c. of pancreatic extract subcutaneously injected.

In the following three examples, adrenalin was injected when the effect of the pancreatic extract had become evident.
Experiment XIV.

Rabbit 22.  1.6 kilos.

Blood sugar before injection 0.116 per cent.
At $9^{\frac{3}{4}}$ a.m., 1 c.c. of pancreatic extract subcutaneously injected.
10h00', blood sugar 0.087 per cent.
10h30', blood sugar 0.146 per cent and 1 c.c. of adrenalin subcutaneously injected.
11h00', blood sugar 0.110 per cent.
11h30', blood sugar 0.146 per cent.
12h30', blood sugar 0.123 per cent.
1h30', blood sugar 0.111 per cent.
2h30', blood sugar 0.092 per cent.
3h30', blood sugar 0.088 per cent.
4h30', blood sugar 0.086 per cent.

Experiment XV.

Rabbit 23.  1.6 kilos.

Blood sugar before injection 0.109 per cent.
At $8^{\frac{3}{4}}$ a.m., 1 c.c. of pancreatic extract subcutaneously injected.
9h10', blood sugar 0.087 per cent.
9h40', blood sugar 0.066 per cent and 1 c.c. of adrenalin subcutaneously injected.
10h10', blood sugar 0.080 per cent.
10h40', blood sugar 0.135 per cent.
11h40', blood sugar 0.116 per cent.
12h40', blood sugar 0.124 per cent.
1h40', blood sugar 0.121 per cent.
2h40', blood sugar 0.110 per cent.
3h40', blood sugar 0.094 per cent.

Experiment XVI.

Rabbit 24.  1.7 kilos.

Blood sugar before injection 0.078 per cent.
At $9^{\frac{1}{2}}$ a.m., 1 c.c. of pancreatic extract subcutaneously injected.
10h10', blood sugar 0.050 per cent and 1 c.c. of adrenalin subcutaneously injected.
10h40', blood sugar 0.091 per cent.
11h10', blood sugar 0.121 per cent.
12h10', blood sugar 0.130 per cent.
1h10', blood sugar 0.127 per cent.
2h10', blood sugar 0.119 per cent.
3h10', blood sugar 0.101 per cent.
4h10', blood sugar 0.081 per cent.

The results of experiments from XIV to XVI are also given in curve form in Figure 10.
Adrenalin Hyperglycemia. IV.

Fig. 10. (Exp. XIV, XV and XVI) first extract and the adrenalin injected.
At the first arrow 1 c.c. of pancreatic extract and at the second arrow 1 c.c. of adrenalin (1:1 000) subcutaneously injected.

In the following three examples 1 c.c. of each of adrenalin and pancreatic extract was injected simultaneously.

Experiment XVII.

Rabbit 25. 1.6 kilos.

Blood before injection sugar 0.101 per cent.
At 10h15' a.m., 1 c.c. adrenalin and 1 c.c. pancreatic extract subcutaneously injected.
10h45', blood sugar 0.073 per cent.
11h15', blood sugar 0.071 per cent.
11h45', blood sugar 0.056 per cent.
12h15', blood sugar 0.051 per cent.
1h15', blood sugar 0.077 per cent.
1h45', blood sugar 0.105 per cent.
Experiment XVIII.

Rabbit 26. 1.7 kilos.

Blood sugar before injection 0.080 per cent.

At 9h10' a.m., 1 c.c. adrenalin and 1 c.c. pancreatic extract subcutaneously injected.

9h40', blood sugar 0.065 per cent.
10h10', blood sugar 0.055 per cent.
10h40', blood sugar 0.043 per cent, mild convulsions.
11h10', blood sugar 0.056 per cent.
11h40', blood sugar 0.072 per cent.
12h10', blood sugar 0.085 per cent.
12h40', blood sugar 0.091 per cent.

Experiment XIX.

Rabbit 27. 1.6 kilos.

Blood sugar before injection 0.089 per cent.

At 8h40' a.m., 1 c.c. adrenalin and 1 c.c. pancreatic extract subcutaneously injected.

9h40', blood sugar 0.079 per cent.
10h10', blood sugar 0.066 per cent.
10h40', blood sugar 0.052 per cent.
10h40', blood sugar 0.053 per cent, convulsions.
11h10', blood sugar 0.062 per cent.
11h40', blood sugar 0.081 per cent.
12h10', blood sugar 0.083 per cent.

Fig. 11. (Exp. XVII, XVIII and XIX) adrenalin and pancreatic extract were injected at the same time.
The results of experiments from XVII to XIX are given in curve form in Figure 11.

In these examples the height of blood sugar decreases until about two hours after the injection, but then it increases gradually, resuming almost the same height of the initial blood sugar in 5-6 hours. It may be inferred from this result that while the hypoglycemic effect of the pancreatic extract passes away in 2-3 hours, as the hyperglycemic effect of the adrenalin lasts longer, it causes the fall of blood sugar in the first part of the course of the change of the blood sugar content and the rise of blood sugar in the latter part.

It is clear, of course, that the type of the change of the blood sugar content varies according to the strength and quantity of the pancreatic extract and the quantity of adrenalin.

In short, so far as blood sugar is concerned, adrenalin and pancreas hormone have reactions diametrically opposite, and each inhibits the other's action. On this point the result of mine coincide with those of Banting and others.

(4) The Effect of Pancreas Hormon on the Hyperglycemia Caused by Piqûre.

The conditions indispensable to produce positive hyperglycemia by pique are a sufficient glycogen supply in liver and the correct position of the puncture. For the purpose of providing the former condition, the rabbits were adminstered with 20-30 grms. of cane-sugar the night before the experiment. And for the latter condition, i.e. in order to puncture at the correct place, while the head of the rabbits was kept bending as far forward as possible, the occipital bone was stripped of its skin and a small hole was made at the occipital tubercle with a small trephine, and then an instrument was pricked in the direction of the outer canthi of the eyes as far as it was felt to come into collision with the basilar process.

And then the accuracy of the puncture was confirmed by autopsy. As a preliminary to each experiment, I examined if the pancreatic extract, which was to be used, surely caused hypoglycemia.

The effect of pique solitary on normal rabbits is shown in the following experiments (Experiment XX-XXII).
Experiment XX.

Rabbit 28. 1.6 kilos.

Blood sugar before puncture 0.100 per cent.
At 9h25' a.m., puncture performed.
  9h55', blood sugar 0.180 per cent.
  10h25', blood sugar 0.202 per cent.
  10h55', blood sugar 0.181 per cent.
  11h25', blood sugar 0.165 per cent.
  11h55', blood sugar 0.168 per cent.
  12h25', blood sugar 0.168 per cent.
  12h55', blood sugar 0.168 per cent.
  1h25', blood sugar 0.136 per cent.
  1h55', blood sugar 0.129 per cent.
  2h10', blood sugar 0.115 per cent.

Animal killed 5 hours after sugar puncture. The liver showed a glycogen content of 0.59 per cent. Puncture situated 3 mm. to the left of the midline and 5 mm. above the calamus scriptorius.

Experiment XXI.

Rabbit 29. 1.6 kilos.

Blood sugar before puncture 0.120 per cent.
At 9h10' a.m., sugar puncture performed.
  9h40', blood sugar 0.160 per cent.
  10h10', blood sugar 0.181 per cent.
  10h40', blood sugar 0.222 per cent.
  11h10', blood sugar 0.260 per cent.
  11h40', blood sugar 0.248 per cent.
  12h10', blood sugar 0.258 per cent.
  12h40', blood sugar 0.240 per cent.
  1h10', blood sugar 0.252 per cent.
  1h40', blood sugar 0.160 per cent.
  3h10', blood sugar 0.139 per cent.

Puncture situated in midline and 10 mm. above calamus scriptorius, the liver glycogen not determined.

Experiment XXII.

Rabbit 30. 1.7 kilos.

Blood sugar before puncture 0.100 per cent.
At 9h40' a.m., puncture performed.
  10h10', blood sugar 0.150 per cent.
  10h40', blood sugar 0.238 per cent.
  11h10', blood sugar 0.251 per cent.
  11h40', blood sugar 0.241 per cent.
  12h10', blood sugar 0.231 per cent.
  12h40', blood sugar 0.200 per cent.
  1h10', blood sugar 0.200 per cent.
  1h40', blood sugar 0.168 per cent.
  2h10', blood sugar 0.150 per cent.
  2h40', blood sugar 0.140 per cent.
  3h10', blood sugar 0.148 per cent.

Puncture situated 2 mm. to the sight of midline and 7 mm. above the calamus scriptorius. Animal killed 6 hours after puncture. The liver showed 0.34 per cent glycogen.
The results of piqure are given in curve form in Figure 12.

![Graph showing blood sugar levels over time for three rabbits](image)

Fig. 12. (Exp. XX, XXI and XXII). At the arrow piqure performed.

In short, the piqure causes blood sugar to rise very rapidly. Then I observed what influence the pancreatic extract has on hyperglycemia caused by piqure.

In the first group of rabbits, the pancreatic extract was injected subcutaneously first, and 60 minutes after it piqure was performed.

**Experiment XXIII.**

Rabbit 31. 1.8 kilos.

Blood sugar before injection 0.120 per cent.
At 11h10' a.m., 1 c.c. of pancreatic extract subcutaneously injected.
11h40', blood sugar 0.100 per cent.
12h10', blood sugar 0.080 per cent, piqure performed.
12h40', blood sugar 0.066 per cent.
1h10', blood sugar 0.056 per cent.
2h40', blood sugar 0.054 per cent.
3h10', blood sugar 0.040 per cent, convulsions.
3h40', blood sugar 0.035 per cent.
4h10', animal moribund, blood sugar 0.024 per cent.

Animal died 3 hours after piqure. No glycogen in the liver found. Puncture situated in midline and 7 mms. above calamus scriptorius.
Experiment XXIV.

Rabbit 32. 1.7 kilos.

Blood sugar before injection 0.100 per cent.
At 10h00' a.m., 1 c.c. of pancreatic extract subcutaneously injected.
10h30', blood sugar 0.082 per cent.
11h30', blood sugar 0.070 per cent, piqure performed.
11h30', blood sugar 0.082 per cent.
12h00', blood sugar 0.079 per cent.
12h30', blood sugar 0.074 per cent.
1h00', blood sugar 0.061 per cent.
1h30', blood sugar 0.055 per cent, animal very weak and excitable.
2h00', blood sugar 0.039 per cent; convulsions.
2h30', animal was killed by a blow on the neck.
Animal died 3½ hours after piqure. The glycogen is found in the liver in trace. Puncture situated 3 mm. to the left of the midline and 5 mm. above calamus scriptorius.

Experiment XXV.

Rabbit 33. 1.7 kilos.

Blood sugar before injection 0.105 per cent.
At 9h30' a.m., 1 c.c. of pancreatic extract subcutaneously.
10h00', blood sugar 0.075 per cent.
10h30', blood sugar 0.059 per cent and piqure performed.
11h00', blood sugar 0.074 per cent.
11h30', blood sugar 0.085 per cent.
12h00', blood sugar 0.070 per cent.
1h00', blood sugar 0.066 per cent.
2h00', blood sugar 0.060 per cent.
2h30', blood sugar 0.046 per cent.
3h00', blood sugar 0.060 per cent.
10h00' a.m. next day, blood sugar 0.093 per cent.
Animal was killed 23½ hours after piqure. The glycogen content of the liver showed 0.42 per cent. Puncture situated in midline and 6 mm. above calamus scriptorius.

The results of experiments from XXIII to XXV are given in curve form in Figure 13.
Adrenalin Hyperglycemia. IV.

At the first arrow 1 c.c. of pancreatic extract injected and at the second arrow puncture performed.

In the second group of rabbits, the sugar puncture was performed first and the pancreatic extract was injected subcutaneously (Experiment XXVI–XXVIII).

**Experiment XXVI.**

Rabbit 34. 1.5 kilos.

Blood sugar before puncture 0.082 per cent.

At 9h15' a.m., puncture performed.

9h45', blood sugar 0.182 per cent.

10h15', blood sugar 0.202 per cent, 1 c.c. of pancreatic extract subcutaneously injected.

10h45', blood sugar 0.160 per cent.

11h15', blood sugar 0.148 per cent.

11h45', blood sugar 0.108 per cent.

12h15', blood sugar 0.070 per cent.

12h45', blood sugar 0.040 per cent, convulsions.

1h15', blood sugar 0.036 per cent.

Animal died 3½ hours after injection of extract, and 4½ hours after puncture. Liver glycogen not determined. Puncture situated 3 mms. to the right of midline and 5 mms. above calamus scriptorius.
Experiment XXVII.

Rabbit 35. 1.7 kilos.

Blood sugar before piqué 0.092 per cent.
At 9h35’ a.m., piqué performed.

10h05’, blood sugar 0.168 per cent.
10h35’, blood sugar 0.192 per cent and 1 c.c. of pancreatic extract subcutaneously injected.
11h05’, blood sugar 0.146 per cent.
11h35’, blood sugar 0.140 per cent.
12h05’, blood sugar 0.112 per cent.
12h35’, blood sugar 0.100 per cent.

2h00’, animal moribund, blood sugar 0.025 per cent.

Animal died 3½ hours after injection of extract and 4½ hours after piqué. Liver glycogen not determined. Puncture situated 2 mms. to the left of midline and 10 mms. above calamus scriptorius.

Experiment XXVIII.

Rabbit 36. 1.8 kilos.

Blood sugar before piqué 0.100 per cent.
At 8h55’ a.m., piqué performed.

9h25’, blood sugar 0.152 per cent.
9h55’, blood sugar 0.161 per cent, and 1 c.c. of pancreatic extract subcutaneously injected.
10h25’, blood sugar 0.190 per cent.
10h55’, blood sugar 0.178 per cent.
11h25’, blood sugar 0.142 per cent.
11h55’, blood sugar 0.100 per cent.
12h25’, blood sugar 0.100 per cent.
1h25’, blood sugar 0.060 per cent.

1h55’, blood sugar 0.040 per cent, convulsions.

Animal became moribund 4 hours after injection of extract and the liver showed a glycogen content of 0.31 per cent. Puncture situated in midline and 7 mms. above calamus scriptorius.

The results of experiments from XXVI of XXVIII are given in curve form in Figure 14.
Adrenalin is one of the most powerful and quickest of raising the blood pressure. If the pancreatic extract and adrenalin are antagonistic to each other in their actions, the pancreatic extract must lower not only the blood pressure in normal condition but also that which has been raised by adrenalin. According to Klemperer and others, the pancreatic extract lowers the blood pressure of diabetics and hypertonics.

In some experiments in our Laboratory, when the pancreatic extract not yet purified sufficiently was applied, it caused a very transient fall of blood pressure.

But in other experiments, when the purified pancreatic extract was applied, neither the normal blood pressure nor the blood pressure raised by adrenalin was influenced by the extract. This result is conformable to that of Collazo, Händel and Grevenstuk, Laquer and Riebensahm.
(6) **The Effect of Pancreatic Extract on the Peripheral Blood Vessels.**

Ringer's solution was perfused through the blood vessels of the hind-quarters of bull-frogs by Trendelenburg's method and the pancreatic extract was added to it and measured the change of the rate of the outflow. Yet they had no influence not only on the blood vessels in normal condition but also on the vessels contracted with adrenalin beforehand (Tab. I and II).

**Table I.**

*The perfusion experiments with Trendelenburg's method.*

In each experiment, 0.5 c.c. pancreatic extract of acid reaction injected.

<table>
<thead>
<tr>
<th>No. of Experiment</th>
<th>Before injection</th>
<th>Time after injection and number of drops</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1' 2' 3' 4' 5' 10' 15' 20' 25' 30'</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>40 drops</td>
<td>38 37 38 39 40 40 39 40 40</td>
<td>40 to 37 decreased</td>
</tr>
<tr>
<td>b</td>
<td>40 drops</td>
<td>39 38 37 38 39 40 40 40 40</td>
<td>40 to 37 decreased</td>
</tr>
<tr>
<td>c</td>
<td>42 drops</td>
<td>42 41 42 42 41 42 42 42 41 42</td>
<td>no change</td>
</tr>
<tr>
<td>II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>37 drops</td>
<td>36 36 37 36 37 37 37 37 36 37</td>
<td>no change</td>
</tr>
<tr>
<td>b</td>
<td>39 drops</td>
<td>39 39 38 37 37 39 39 39 38 39</td>
<td>no change</td>
</tr>
<tr>
<td>c</td>
<td>33 drops</td>
<td>32 32 32 32 32 32 32 32 32 32</td>
<td>no change</td>
</tr>
<tr>
<td>III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>45 drops</td>
<td>39 34 30 32 34 38 38 44 43 44</td>
<td>slightly diminished</td>
</tr>
<tr>
<td>b</td>
<td>38 drops</td>
<td>35 34 36 37 38 38 37 38 38 37</td>
<td>very slightly diminished</td>
</tr>
<tr>
<td>c</td>
<td>42 drops</td>
<td>40 38 40 40 41 41 42 41 42 42</td>
<td>very slightly diminished</td>
</tr>
</tbody>
</table>

**Table II.**

*The perfusion experiments with Trendelenburg's method.*

In each experiment, 0.5 c.c. pancreatic extract neutralized with sodium carbonate injected.

<table>
<thead>
<tr>
<th>No. of Experiment</th>
<th>Before injection</th>
<th>Time after injection and number of drops</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1' 2' 3' 4' 5' 10' 15' 20' 25' 30'</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>28 drops</td>
<td>25 27 26 27 28 28 28 27 29 28</td>
<td>no change</td>
</tr>
<tr>
<td>b</td>
<td>35 drops</td>
<td>35 33 33 34 34 35 35 34 35 35</td>
<td>no change</td>
</tr>
<tr>
<td>c</td>
<td>36 drops</td>
<td>34 34 34 35 36 35 36 36 35 35</td>
<td>no change</td>
</tr>
<tr>
<td>II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>40 drops</td>
<td>39 39 40 39 41 40 39 40 40 41</td>
<td>no change</td>
</tr>
<tr>
<td>b</td>
<td>42 drops</td>
<td>42 42 41 43 42 42 42 42 42 42</td>
<td>no change</td>
</tr>
<tr>
<td>c</td>
<td>39 drops</td>
<td>39 39 38 39 40 39 38 39 39 39</td>
<td>no change</td>
</tr>
<tr>
<td>III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>40 drops</td>
<td>38 36 36 38 38 40 39 40 39 40</td>
<td>slightly diminished</td>
</tr>
<tr>
<td>b</td>
<td>38 drops</td>
<td>36 36 37 38 38 39 38 37 38 38</td>
<td>very slightly diminished</td>
</tr>
<tr>
<td>c</td>
<td>38 drops</td>
<td>37 38 38 39 37 38 37 38 38 39</td>
<td>no change</td>
</tr>
</tbody>
</table>
(7) The Effect of the Pancreatic Extract on the Pupils.

In both normal and depancreatized dogs, the pancreatic extract does not influence the pupils. It does not influence the enucleated eye-pupils of frogs too (Tab. III–VIII).

**Table III.**

*Effect of pancreatic extract on the pupil of the depancreatized dogs.*

<table>
<thead>
<tr>
<th>Date</th>
<th>No. of dog</th>
<th>I.</th>
<th>II.</th>
<th>III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before operation</td>
<td></td>
<td>no effect</td>
<td>no effect</td>
<td>no effect</td>
</tr>
<tr>
<td>1 day after operation</td>
<td></td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>2 days &quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>5 days &quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
</tbody>
</table>

**Table IV.**

*Effect of pancreatic extract upon the enucleated eye-pupils of frogs.*

<table>
<thead>
<tr>
<th>Time</th>
<th>Side of test</th>
<th>Control side</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Longitudinal diameter</td>
<td>Transverse diameter</td>
</tr>
<tr>
<td>Before instillation</td>
<td>3.0 mms.</td>
<td>2.0 mms.</td>
</tr>
<tr>
<td>1h 00’</td>
<td>unchanged</td>
<td>unchanged</td>
</tr>
<tr>
<td>1h 10’ after instillation</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>1h 30’</td>
<td>3.0 mms.</td>
<td>3.0 mms.</td>
</tr>
<tr>
<td>2h 00’</td>
<td>slight but visible dilation</td>
<td>as above</td>
</tr>
<tr>
<td>2h 30’</td>
<td>as above</td>
<td>as above</td>
</tr>
<tr>
<td>3h 00’</td>
<td>as above</td>
<td>as above</td>
</tr>
</tbody>
</table>
**TABLE V.**

*Effect of pancreatic extract upon the enucleated eye-pupils of frogs.*

<table>
<thead>
<tr>
<th>Time</th>
<th>Side of test</th>
<th>Control side</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Longitudinal</td>
<td>Transverse</td>
</tr>
<tr>
<td></td>
<td>diameter</td>
<td>diameter</td>
</tr>
<tr>
<td>Before instillation</td>
<td>2.5 mms.</td>
<td>2.0 mms.</td>
</tr>
<tr>
<td>10' after instillation</td>
<td>no change</td>
<td>no change</td>
</tr>
<tr>
<td>30' after instillation</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>1 hour after instillation</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>2 hours after instillation</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
</tbody>
</table>

2 drops of undiluted pancreatic extract instilled.

**TABLE VI.**

*Effect of pancreatic extract upon the adrenalin mydriasis in frogs.*

<table>
<thead>
<tr>
<th>Time</th>
<th>Side of test</th>
<th>Control side</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Longitudinal</td>
<td>Transverse</td>
</tr>
<tr>
<td></td>
<td>diameter</td>
<td>diameter</td>
</tr>
<tr>
<td>Before instillation</td>
<td>3.0 mms.</td>
<td>2.0 mms.</td>
</tr>
<tr>
<td>15:20'</td>
<td>2 drops of adrenalin instilled.</td>
<td></td>
</tr>
<tr>
<td>15:30' after instillation</td>
<td>Pupil slightly dilated</td>
<td>no change</td>
</tr>
<tr>
<td>15:50'</td>
<td>3.0 mms.</td>
<td>3.0 mms.</td>
</tr>
<tr>
<td>&quot;</td>
<td>Pupil almost round shaped</td>
<td></td>
</tr>
<tr>
<td>21:20'</td>
<td>4.0 mms.</td>
<td>3.0 mms.</td>
</tr>
<tr>
<td>&quot;</td>
<td>Pupil almost maximal dilated</td>
<td></td>
</tr>
<tr>
<td>21:30'</td>
<td>2 drops of pancreatic extract instilled</td>
<td></td>
</tr>
<tr>
<td>21:40'</td>
<td>Pupil maximal still</td>
<td>&quot;</td>
</tr>
<tr>
<td>21:50'</td>
<td>as above</td>
<td>&quot;</td>
</tr>
<tr>
<td>3:00'</td>
<td>as above</td>
<td>&quot;</td>
</tr>
<tr>
<td>3:30'</td>
<td>Pupil became opaque</td>
<td>&quot;</td>
</tr>
</tbody>
</table>
**TABLE VII.**

*Effect of pancreatic extract upon the adrenalin mydriasis in frogs.*

<table>
<thead>
<tr>
<th>Time</th>
<th>Side of test</th>
<th>Control side</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Longitudinal diameter</td>
<td>Transverse diameter</td>
</tr>
<tr>
<td>Before instillation</td>
<td>2.0 mms.</td>
<td>1.5 mms.</td>
</tr>
<tr>
<td>2h 15' after instillation</td>
<td>2 drops of adrenalin instillated</td>
<td>no change</td>
</tr>
<tr>
<td>2h 45'</td>
<td>no change</td>
<td>no change</td>
</tr>
<tr>
<td></td>
<td>began to dilate</td>
<td></td>
</tr>
<tr>
<td>3h 15'</td>
<td>3.0 mms.</td>
<td>3.0 mms.</td>
</tr>
<tr>
<td></td>
<td>pupil round shaped</td>
<td></td>
</tr>
<tr>
<td>3h 45'</td>
<td>2 drops of pancreatic extract instillated</td>
<td>&quot;</td>
</tr>
<tr>
<td>3h 50'</td>
<td>unchanged and maximal wide still</td>
<td>&quot;</td>
</tr>
<tr>
<td>4h 00'</td>
<td>as above</td>
<td>&quot;</td>
</tr>
<tr>
<td>5h 00'</td>
<td>Pupil became opaque</td>
<td>&quot;</td>
</tr>
</tbody>
</table>

**TABLE VIII.**

*First pancreatic extract and then adrenalin are instillated.*

<table>
<thead>
<tr>
<th>Time</th>
<th>Side of test</th>
<th>Control side</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Longitudinal diameter</td>
<td>Transverse diameter</td>
</tr>
<tr>
<td>Before instillation</td>
<td>2.5 mms.</td>
<td>2.0 mms.</td>
</tr>
<tr>
<td>9h 20' after instillation</td>
<td>2 drops of pancreatic extract instillated</td>
<td>no change</td>
</tr>
<tr>
<td>10h 20'</td>
<td>no change</td>
<td>no change</td>
</tr>
<tr>
<td>10h 25'</td>
<td>2 drops of adrenalin instillated</td>
<td>&quot;</td>
</tr>
<tr>
<td>10h 40'</td>
<td>3.0 mms.</td>
<td>2.0 mms.</td>
</tr>
<tr>
<td>11h 10'</td>
<td>Pupil almost maximal dilated</td>
<td>&quot;</td>
</tr>
</tbody>
</table>
It is a well known fact, that adrenalin causes the relaxation of the intestinal movements. When a few drops of our pancreatic extract, which is acid in reaction, is added to Ringer's solution of 30 c.c., in which a strip of isolated small intestine is suspended, its movements are temporarily inhibited. After 2–3 minutes the movements are gradually restored, its amplitude developing a tendency to grow larger than before (Fig. 15).

This phenomenon will possibly be due to acid reaction of our extract. On the other hand, when the solution is made slightly alkaline in reaction, the intestine is caused to contract (Fig. 16).
The precipitate of the pancreatic extract, which is formed by $P_{II} 5-6$, is not easily soluble in Ringer’s solution. The precipitate is mixed in Ringer’s solution, so as to make a suspension, and when 0.5 of such suspension is given to a rabbit subcutaneously, the blood sugar falls from 0.084 to 0.038 per cent within two hours, and death follows with convulsion. When the suspension is separated by means of a centrifuge and 0.5 c.c. of its upper clear fluid is administered to a rabbit subcutaneously, the blood sugar, though slight in degree, falls down also: 0.110 per cent of the blood sugar of a rabbit before injection falls to 0.043 within three hours, rising again to the normal blood sugar content. This fact seems to indicate, that the precipitate of our pancreatic extract, however small the quantity may be, is soluble in Ringer’s solution, but such a solution has no influence upon the movements of intestinal strip; that is, the pancreatic extract has no effect upon intestinal movements (Fig. 17).

![Fig. 17. Tracing showing the action of pancreatic extract solved in Ringer's fluid upon the intestinal movements of a rabbit. Base line 6 seconds. At asterisk 10 drops of pancreatic extract solved in Ringer's fluid is added.](image1)

The same action is observed with the insulin-Lilly from America (Fig. 18).

![Fig. 18. Tracing showing the action of insulin Lilly from America on the intestinal contractions of a rabbit. The time is marked in 5 seconds. At asterisk 10 drops of insulin is added.](image2)
(9) Pituitrin and Pancreatic Extract.

In 1886 Marie reported that acromegaly was connected with hypophysis in some way. Afterward von Noorden, Borchardt and others reported that glycosuria came out with extraordinary frequency associated with acromegaly. And hypophysis was supposed to have any influence, direct or indirect, on carbohydrate metabolism. But the results of the experimental researches which were intended to work out this supposition, were very discordant. Many of these experiments did not produce any sufficient evidence to support this supposition, but rather some of the evidences tended to deny it.

The summary of its chief literature may be mentioned below.
Borchardt observed that the extracts of horse or human hypophyses caused transient glycosuria in rabbits but he failed to demonstrate it in dogs.
Franchini obtained entirely negative results. Falta, Newburgh and Nobel found that the extract of pituitary body does not produce glycosuria in either dogs or rabbits.
Goetsch, Cushing and Jacobson saw that the extract caused glycosuria regularly and Kepinow reported that pituitrin could augment the vaso-motor and mydriatic effects of adrenalin.
Most recently Burn reported that the subcutaneous injection of the extract of posterior lobe of the pituitary gland diminished or abolished the fall of blood sugar caused by insulin.
What influence pituitrin has on the fall of blood sugar caused by our pancreatic extract was observed in the following experiments.
Pituitrin when injected by itself, causes the rise of blood sugar, but the rise is very slight and transient.
According to Burn, the simultaneous injection of pituitary extract and insulin diminishes or abolishes the fall of blood sugar caused by an injection of insulin, though this effect of pituitary extract can not be explained by its power, of producing an increase of the blood sugar which, is so slight that, when taken mathematically, should not compensate for the fall produced by insulin.
But in my experiment, such a phenomenon was not observed (Experiment XXIX–XXXII).
Experiment XXIX.

Rabbit 1. 1.4 kilos.
0.2 c.c. of pancreatic extract alone subcutaneously injected.

<table>
<thead>
<tr>
<th>Time of taking blood</th>
<th>Blood sugar (per cent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before injection</td>
<td>0.112</td>
</tr>
<tr>
<td>15' after injection</td>
<td>0.110</td>
</tr>
<tr>
<td>30'</td>
<td>0.093</td>
</tr>
<tr>
<td>1 hr.</td>
<td>0.082</td>
</tr>
<tr>
<td>2 hrs.</td>
<td>0.059</td>
</tr>
<tr>
<td>3 hrs.</td>
<td>0.048; convulsions</td>
</tr>
<tr>
<td>4 hrs.</td>
<td>0.033; died</td>
</tr>
</tbody>
</table>

Experiment XXX.

Rabbit 2. 1.5 kilos.
1 c.c. of pituitrin alone subcutaneously injected.

<table>
<thead>
<tr>
<th>Time of taking blood</th>
<th>Blood sugar (per cent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before injection</td>
<td>0.112</td>
</tr>
<tr>
<td>15' after injection</td>
<td>0.155</td>
</tr>
<tr>
<td>30'</td>
<td>0.136</td>
</tr>
<tr>
<td>1 hr.</td>
<td>0.119</td>
</tr>
<tr>
<td>2 hrs.</td>
<td>0.117</td>
</tr>
<tr>
<td>3 hrs.</td>
<td>0.110</td>
</tr>
<tr>
<td>5 hrs.</td>
<td>0.100</td>
</tr>
</tbody>
</table>

Experiment XXXI.

Rabbit 3. 1.7 kilos (for 24 hours starved).
0.2 c.c. of pancreatic extract and 1 c.c. of pituitrin were subcutaneously injected at the same time (12:35' p.m.).

<table>
<thead>
<tr>
<th>Time of taking blood</th>
<th>Blood sugar (per cent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before injection</td>
<td>0.110</td>
</tr>
<tr>
<td>15' after injection</td>
<td>0.107</td>
</tr>
<tr>
<td>30'</td>
<td>0.100</td>
</tr>
<tr>
<td>1 hr.</td>
<td>0.086</td>
</tr>
<tr>
<td>2 hrs.</td>
<td>0.071</td>
</tr>
<tr>
<td>3 hrs.</td>
<td>0.055</td>
</tr>
<tr>
<td>4 hrs.</td>
<td>0.049; dyspnoic and hyperexcitable</td>
</tr>
<tr>
<td>5 hrs.</td>
<td>0.040; convulsions and died.</td>
</tr>
</tbody>
</table>
Experiment XXXII.

Rabbit 4. 1.3 kilos (for 24 hours starved.)

0.2 c.c. of pancreatic extract and 1.5 c.c. of pituitrin were subcutaneously injected at the same time (10h23' a.m.).

<table>
<thead>
<tr>
<th>Time of taking blood</th>
<th>Blood sugar (per cent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before injection</td>
<td>0.097</td>
</tr>
<tr>
<td>15' after injection</td>
<td>0.095</td>
</tr>
<tr>
<td>30'</td>
<td>0.089</td>
</tr>
<tr>
<td>1 hr.</td>
<td>0.060</td>
</tr>
<tr>
<td>2 hrs.</td>
<td>0.045; convulsions</td>
</tr>
<tr>
<td>3 hrs.</td>
<td>0.040</td>
</tr>
<tr>
<td>3 hrs. 45'</td>
<td>0.020; died.</td>
</tr>
</tbody>
</table>

While pituitrin, as very well known stimulate the contraction of the uterine stripe, the pancreatic extract has no influence on the normal uterine contraction and the contracted uterine stripe with pituitrin (Fig. 19 and 20).

![Uterine contraction of a cat](image)

Fig. 19. Tracing showing the action of the extract upon the normal uterine contraction in a cat.
At asterisk 10 drops of pancreatic extract is added.

SUMMARY AND DISCUSSION.

According to the polyglandular doctrine the functions of adrenals must be related in some way with those of pancreas. Herter and Richards\(^ {23} \) found intensive glycosuria and lesions of the islands of Langerhans after painting adrenalin on pancreas.
Herter and Wakeman\textsuperscript{24}) repeated the same experiment and thought lesions of islands to be of accidental character.

Lazarus\textsuperscript{25}) observed some increase of the islands of Langerhans by repeated adrenalin injections into guinea-pigs. But Herxheimer\textsuperscript{26}) failed to demonstrate such a change even after five months of repeated injections of adrenalin. If adrenalin produces its glycosuric effect by any action upon the internal secretion of the pancreas, the following mechanisms are possible: adrenalin might act upon the pancreas by injuring the cells of pancreas directly, by inhibiting their activity by way of nervous influence and circulation and lastly by neutralizing or destroying the internal secretion of the pancreas. These possibilities are clearly excluded by the fact that the adrenalin glycosuria can occur even in the absence of the pancreas as in the experiments of Noel-Paton\textsuperscript{27}) and Doyon, Morel and Kareff.\textsuperscript{28}) Frank and Isaac\textsuperscript{29}) claimed that the effect of adrenalin is far more powerful in the depancreatized animals than in the normal animals.

The majority of evidences shows that adrenals have no direct connection whatever with the pancreas.

In my experiments with purified and powerful pancreatic extract also, there is no evidence of any specific antagonism between the adrenlin and the pancreas hormone.
CONCLUSIONS.

1. The pancreatic extract suppresses the adrenalin hyperglycemia when the dose of the latter is not too much. But this effect of the pancreatic extract is not specific only to the adrenalin glycosuria, because it is capable of lowering the blood sugar in normal animals and in other experimental hyperglycemia.

2. The pancreatic extract takes more powerful effect in the subcutaneous injection than in the intravenous application.

3. The pancreatic extract has no influence upon the normal blood pressure and can not lower the pressure raised previously with adrenalin.

4. The artificial perfusion of the extract through the peripheral blood vessels by the Laewen-Trendelenburg's method causes no change in the rate of the outflow of Ringer's solution.

5. The extract produces no change in the enucleated frog's-eye-pupil both in normal state and in adrenalin mydriasis. It has no effect on the pupils of dogs either normal or depancreatized.

6. The rectal temperature scarcely undergoes a change until collapse occurs.

7. The rise of blood sugar caused by piqure is powerfully reduced by the subcutaneous injection of the extract.

8. The pancreatic extract in acid reaction inhibits the movements of intestine, but this phenomenon is probably to attribute to acid reaction of the extract and the substance itself, which causes the fall of the blood-sugar, has no effect upon the intestinal movements.

9. Pituitrin has no obvious inhibiting influence upon the fall of blood sugar caused by the pancreatic extract.

10. The pancreatic extract causes no effect upon the contraction of the surviving uterus-strip of the cat either in normal condition or in condition contracted with adrenalin.

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Prof. Dr. T. Kumagai.