EXPERIMENTAL DIABETES CAUSED BY 1-(2-QUINOLYL)-3-METHYL-5-PYRAZOLONE

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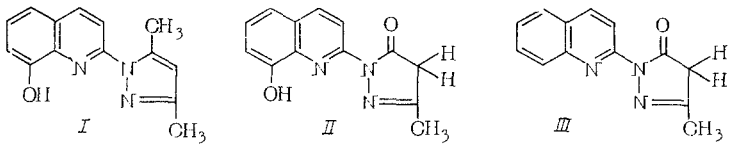
Intravenous injection of 1-(2-quinolyl)-3-methyl-5-pyroazolone into rabbits causes the development of a permanent and severe diabetes as the result of selective damage to the pancreatic islets of Langerhans.

It was shown previously that some chemical compounds with chelating ability can produce permanent diabetes in rabbits [1-9]. By comparing compounds with different chemical structure but possessing the ability to form stable complexes with metals some progress may be made toward elucidating the causes of the diabetogenic action of chelating agents.

The following pyrazole derivatives were studied in the present investigation:

1-(8-hydroxy-2-quinolyl)-3,5-dimethylpyrazolone (I)
1-(8-hydroxy-2-quinolyl)-3-methyl-5-pyrazolone (II), and
1-(2-quinolyl)-3-methyl-5-pyrazolone (III).



Two of these compounds (I and II) had not previously been investigated; with regard to III very limited information is available in only one paper [10].

EXPERIMENTAL

Each of the test substances was dissolved in 0.1 N NaOH with heating, filtered, cooled to body temperature, and injected slowly into the auricular vein of rabbits preliminarily starved for 2 days. Compound I is only sparingly soluble, but II and III are much more soluble. The criterion of the presence or absence of diabetogenic action was the blood sugar concentration determined by the Hagedorn–Jensen method. The pancreas was removed from animals which died or were sacrificed at the end of the experiment, and fixed in Bouin's fluid. Sections, 4-5 μ in thickness, were stained with chromehaematoxylin-phloxine and with aldehyde-fuchsine by Gomori's method.

EXPERIMENTAL RESULTS

The largest quantity of compound I which could be injected did not exceed 44 mg/kg. The injection was accompanied by a mild and transient excitation. No changes in the blood sugar level were detected in experiments on three rabbits.

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TABLE 1. Experimental Diabetes Caused by 1-(2-Quinolyl)-3-methyl-5-pyrazolone

Rabbit No.	Wt. of animal (in kg) initial	Wt. of animal (in kg) final	Dose of III (in kg/kg)	Length of survival (in days)	Blood sugar (in mg %) initial*	Blood sugar (in mg %) mean during disease†	Remarks
1	2,03	1,49	100	38	113	513	Dead
2	2,27	2,35	100	35	101	385	
3	2,14	2,65	100	102	145	322	Dead
4	2,44	2,08	100	5	133	343	
5	2,31	1,95	100	50	147	392	
6	2,05	1,63	100	42	107	378	
7	2,32	2,84	110	100	129	206	Dead
8	2,17	1,88	110	6	105	389	"
9	1,88	1,21	110	15	127	473	
10	2,26	1,46	120	39	103	433	Dead
11	1,76	1,52	120	47	133	383	
12	2,90	1,63	143	44	126	470	"

*M ± m = 122 ± 3, P < 0.0001.
†M ± m = 385 ± 27, P < 0.001.

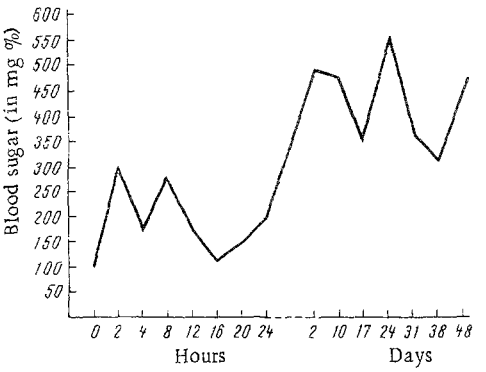

Fig. 1. Changes in blood sugar in rabbit No. 6 with diabetes caused by 1-(2-quinolyl)-3-methyl-5-pyrazolone.

Fig. 2

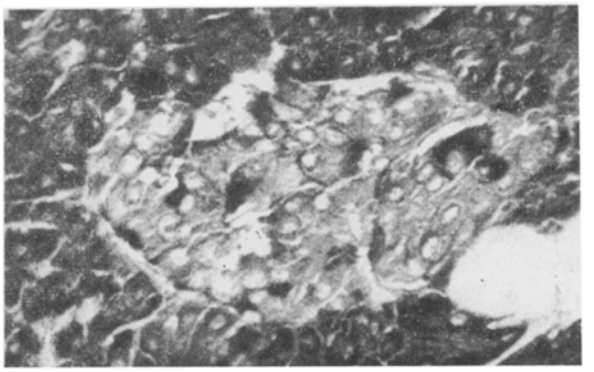

Fig. 3

Fig. 2. Islet of Langerhans during diabetes: A cells (black) occupy a large area of the islet. Hematoxylin-phloxine, 400 ×.

Fig. 3. Islet of Langerhans of rabbit No. 7 which recovered from diabetes: individual B cells contain granules (black). Aldehyde-fuchsine, 400 ×.

Compound II possessed neurotropic activity. A dose of 20-25 mg/kg caused death of 3 of the 4 animals. Immediately after the injection, very strong spasms developed in all muscle groups, with contraction of the spinal muscles, neck rigidity, spasms of the muscles of mastication, and interrupted breathing. The convulsions were repeated and continued for 4-6.5 h. No substantial changes in the blood sugar could be found in the surviving rabbit. Two rabbits received injections of 10-13 mg/kg of compound II in the course of 6-8 days. This dose produced mild and transient convulsions only occasionally. Repeated determination of the blood sugar revealed no appreciable changes. At the end of the experiment the animals were sacrificed by air embolism. In sections stained with aldehyde-fuchsine, no significant changes could be found in the histological structure of the pancreas.

Compound III was injected into 12 rabbits in a dose of 100-143 mg/kg. The phases of the blood sugar curve were studied in one rabbit for 24 h (Fig. 1). The blood sugar reached 296 mg% 2 h after injection of III and remained high for 12 h, after which it fell to normal, to be followed 24 h later by a second hyperglycemia, which changed into permanent diabetes. All 12 rabbits developed permanent diabetes, associated with polyphagia, polyuria, glucosuria, and polydipsia. The blood sugar level was high throughout the period of observation, lasting 5-102 days (Table 1).

Histological investigation showed that the general structure of the pancreas was undisturbed after injection of III, and the normal pattern of the acini was preserved. The number of islets of Langerhans, in cases of severe diabetes, when the animals became greatly emaciated and their blood sugar was highest, did not exceed one or two per field of vision, or even per section. The islets were small, irregular in shape, and had uneven edges. The cytoplasm of many of the A and B cells was vacuolated and their nuclei pycnotic and stained bright red. A cells were predominant in the islets of most (8) rabbits (Fig. 2). Staining with aldehyde-fuchsine revealed degranulation of the B cells. A very small number of B-granules remained in a few islet cells. If the diabetes was less severe, sometimes single B cells with numerous granules could be seen. The manifestations of diabetes disappeared in only one of the rabbits (No. 7), on the 56th day of the experiment. The pancreas contained 4-6 islets per field of vision. Well granulated cells were found in many of them, and this may have accounted for the recovery, because B-cell granules correspond to insulin deposition [6]. Measurement of the area of the islets gave a value of 8065 μ^2 in the control animals and 12,126 μ^2 in the rabbit which recovered.

Investigation of the diabetogenic action of the pyrazolone derivatives thus showed that only one of them, 1-(2-quinolyl)-3-methyl-5-pyrazolone (III), possesses marked diabetogenic activity. The study of the morphological changes in the pancreas of the rabbit which recovered suggests that insulin production in the B cells is much greater than the normal insulin demand. Evidence of this is given by restoration of the normal blood sugar level in rabbit No. 7, whose regenerated B cells contained only a small quantity of insulin (Fig. 3). The diabetes described can be used as an adequate model for the study of mechanisms of disturbances of the endocrine function of the pancreas and further research along these lines is justified.

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