studied. The mean difference between bilirubin levels at 2 and 4 days of age was determined in 100 infants given 25 μg of l-triiodothyronine daily. This mean was compared with a similar mean in 100 controls. l-triiodothyronine significantly depressed the neonatal bilirubin level. The drug may exert its effect by accelerating maturation of glucuronic acid conjugating system.

1. Christensen, J. F., *Acta Pediat.*, 1956, v45, 367.
2. Hsia, D. Y-Y., Hsia, H-H., Gellis, S. S., *J. Lab. Clin. Med.*, 1952, v40, 610.
3. Man, E. B., Pickering, D. E., Walker, J., Cooke, R. E., *Pediatrics*, 1952, v9, 32.
4. Pickering, D. E., Kontaxis, N. E., Benson, R. C., Meechan, R. J., *A.M.A. J. Dis. Child.*, 1958, v95, 616.
5. Van Middlesworth, L., *ibid.*, 1954, v88, 439.
6. Kurland, G. S., Hamolsky, M. W., Freedberg, *J. Clin. Endo.*, 1955, v15, 1355.
7. Peterson, R. E., Pierce, C. E., Wyngaarden, J. B., Vunim, J. J., Brodie, D. B., *J. Clin. Invest.*, 1957, v36, 1301.
8. Harris, R. C., Lucey, J. F., MacLean, J. R., *Pediatrics*, 1958, v21, 875.
9. Johnson, L., Sarmiento, F., Day, R., *A.M.A. J. Dis. Child.*, 1958, v96, 504.

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Diabetogenic Action of Analogues of 8-Hydroxyquinoline. (24942)

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As previously reported(1,2,3), some chelating agents for heavy metals have been shown to be diabetogenic in experimental animals. This effect may be attributed to their destructive action on the pancreatic islet cells by chelating with biologically important metallic ions. Further studies have been continued to detect other diabetogenic chelating chemical substances with structural similarity to 8-hydroxyquinoline. The present report deals with studies on the diabetogenic action of analogues of 8-hydroxyquinoline and derivatives of pteridine and similar structures with metal-binding properties.

Materials and methods. Adult rabbits were used. Blood sugar was determined by Hagedorn-Jensen's method(4) at various intervals after intravenous administration of the compounds. Histologic examination of pancreatic islet cells was performed with Gomori's chromium-hematoxylin phloxine method(5). Analogues of 8-hydroxyquinoline were used as solutions of sodium salts. Derivatives of pteridine were administered as aqueous solutions. Tested compounds and intravenously injected doses were as follows: 1-Hydroxyphenazine 30-60 mg/kg, 6-Hydroxy-m-phenanthroline (5:6-Pyridooxine) 30-70 mg/kg, l-Hydroxyacridine 20 mg/kg, 5-Hydroxybenzo-f-quinoline (5:6-Benzooxine) 30-50 mg/kg, 5, 8-Dihydroxyquinoxaline 50 mg/kg, 4-Hydroxypteridine 20 mg/kg, Isoxanthopterine 20 mg/kg, 2-Amino-4-hydroxypteridine 15-30 mg/kg, Picolinic acid 40-100 mg/kg, Dipicolinic acid 20-40 mg/kg.

Results. 1-Hydroxyphenazine caused a transitory hyperglycemia. However, doses over 60 mg/kg were intolerable, as they showed considerable toxicity. 1-2 hours after injection with doses 50-70 mg/kg of 6-Hydroxy-m-phenanthroline there ensued a remarkable hyperglycemia which returned to normal after 3-4 days (Fig. 1). Histologic examination of the pancreas of one rabbit which died 24 hours after injection revealed necrotic and degenerative changes of beta cells of the islets.

1-Hydroxyacridine also could produce a hyperglycemia as shown in Fig. 1. One rabbit died in convulsion 24 hours after administration of 1-hydroxyacridine (blood sugar 26 mg/100 ml). Histologic appearance of the islet of this animal showed degenerative changes of beta cells, while alpha cells remained almost normal. 5-Hydroxybenzo-f-quinoline caused similar hyperglycemia. However, degree of hyperglycemia was somewhat slighter than those produced with above 2

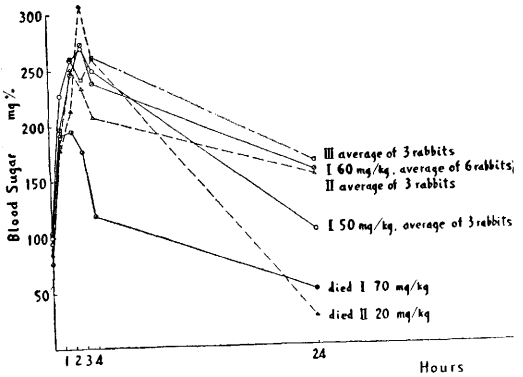

FIG. 1. Changes in blood sugar level in rabbits after intrav. administration of analogues of 8-hydroxyquinoline. I. 6-Hydroxy-m-phenanthroline, II. 1-Hydroxyacridine, III. 5-Hydroxybenzo-f-quinoline.

compounds. After administration of 5,8-dihydroxy-quinoxaline no fluctuation of blood sugar was observed. Three derivatives of pteridine and dipicolinic acid caused no noticeable change in blood sugar with given doses. Picolinic acid showed only a slight hyperglycemic tendency.

Discussion. For elucidating the acting mechanism of diabetogenic substances, it may be important to study the correlation between chemical structures and biological action. Selective affinity of chelating agents for zinc in the islet cells seems to be a clue for the problem. The data presented above show clearly the diabetogenic action of 1-hydroxyacridine, 6-hydroxy-m-phenanthroline and 5-hydroxybenzo-f-quinoline. These compounds have sensitive chelating activity for trace metals, as shown by Albert(6). Therefore, the action of these compounds is presumed to be a result of chelation with zinc ions in the islet cells. Despite its sensitive chelating avidity(7), 5,8-dihydroxy-quinoxaline had no effect on blood sugar. It may be considered, as in quinoline derivatives(3), that addition of hydroxy groups in the compound deprives it of the biological action.

Considering analogous structures to 8-hydroxyquinoline and chelating activity of pteridine derivatives(8), diabetogenic action of some derivatives of pteridine was expected. However, these compounds did not affect blood sugar. Hörlein(9) reported that intravenous administration of xanthopterine into rabbits in doses 20-50 mg/kg caused destruction of kidney and hyperglycemia during a few days after injection. Albert(8) showed that 4-hydroxypteridine, in spite of its structural similarity to 8-hydroxyquinoline, had a far lower affinity for metallic ions. The lack of diabetogenic effect of pteridine derivatives might have been due to poor solubility and lower chelating affinity for metals.

Despite their chelating affinity(10,11), picolinic acid and dipicolinic acid had no diabetogenic action, probably due to the presence of the carboxyl group, as in the case of quinaldinic acid(1). Therefore, available evidence indicates the existence of the essential chemical structures and properties required for diabetogenic action. Besides chelating affinity for trace metals, suitable solubility and property seem to be essential. Much more evidence may be necessary to disclose the possible mechanism of diabetogenic substances.

Summary. 6-Hydroxy - m - phenanthroline and 1-hydroxyacridine caused hyperglycemia and destructive changes of the pancreatic islet in rabbits. 5-Hydroxybenzo-f-quinoline also produced a considerable hyperglycemia. However, 3 derivatives of pteridine, picolinic acid and dipicolinic acid failed to produce significant changes in blood sugar.

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1. Kadota, I., *J. Lab. and Clin. Med.,* 1950, v35, 568.
2. Kadota, I., Midorikawa, O., *ibid.,* 1951, v38, 671.
3. Kadota, I., Abe, T., *ibid.,* 1954, v43, 375.
4. Hagedorn, H. G., Jensen, B. N., *Biochem. Z.,* 1923, v153, 46.
5. Gomori, G., *Am. J. Path.,* 1939, v15, 497.
6. Albert A., Magrath, D., *Biochem. J.,* 1947, v41, 534.
7. Kawai, S., Kimura, K., Furuhata, T., *Proc. Japan Acad.,* 1953, v29, 344.
8. Albert, A., *Biochem. J.,* 1953, v54, 646.
9. Hörlein, H., *Arch. Exp. Path. u. Pharmakol.,* 1941, v198, 258.
10. Suzuki, K., Yasuda, M., Yamazaki, K., *J. Phys. Chem.,* 1957, v61, 229.
11. Suzuki, K., Yamazaki, K., *Naturwissenschaften,* 1957, v14, 396.

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