Plasma immunoreactive glucagon (IRG) represents a family of compounds with different molecular weights. Although the physiologic role of these fractions is largely unknown, their relative abundance may vary under different physiologic and pathologic conditions. This paper describes the pattern of IRG components in normal subjects and in patients with renal failure, diabetes mellitus, glucagonoma and other conditions. The role of the kidneys and of the liver in the metabolism of glucagon is reviewed and discussed.

It has recently been recognized that immunoreactive glucagon (IRG) circulates in a number of different forms in both normal subjects and patients with a variety of disorders. The components of IRG differ in their contribution to total circulating glucagon immunoreactivity in various conditions and in different animal species. At present the significance of these fractions is uncertain. Thus, their relationship to native pancreatic glucagon, biologic potency, response to stimuli, molecular size and even nomenclature are still debated. The overall picture is confused further by the use of different glucagon antisera, which react variably with each circulating immunoreactive glucagon fraction.

Patterns in Normal Subjects

In the initial years after the glucagon radioimmunoassay was established, it was believed that the hormone circulated as a single component with a molecular weight of 3500 daltons. Subsequent studies by Weir et al. (47) and Valverde et al. (44) showed that IRG in the plasma of normal and diabetic subjects was heterogeneous. The IRG eluted in two fractions, namely a high molecular weight component in the globulin region of the column and 3500 dalton glucagon. As the relationship of this high molecular weight material to the 3500 dalton glucagon was uncertain, it was named big-plasma glucagon (B.P.G) or "interference factor", suggesting that it might be an immunologically crossreacting peptide sequence in...
an unrelated protein, possibly a gamma-globulin. However, the possibility re-
mained that it might be closely related to glucagon, either in the form of a pro-
hormone or as a result of binding of glucagon to an unidentified large molecular
weight protein. Valverde, et al. (42) identified four glucagon immunoreactive
fractions in healthy and diabetic dogs, with molecular weights of <20,000,
approximately 9000, 3500 and <2000 daltons. Although the concentrations of the
void volume and 2000 molecular weight fractions were relatively constant, both the
3500 and 9000 dalton components increased markedly in response to phloridzin-
induced hypoglycemia. These four components were also found in normal, diabetic
and pancreatectomized dogs, in which the source of IRG measured with the 30-K
antiserum is the A cells present in the proximal gastrointestinal tract.

Fig. 1. Elution patterns of plasma immunoreactive glucagon (IRG) on 1 x 50 cm
Bio-Gel P-30 columns in 1 control subject and 6 diabetic patients. Vo = void
volume (m. w. <40,000), P = proinsulin (m. w. 9000), G = pancreatic glucagon
(m. w. 3500). All columns were calibrated with 125I-gamma globulin, 131I-pro-
insulin and 125I-glucagon. In panel 6, 1500 pg/ml represents a spurious value
due to the presence of glucagon antibodies. 0----0 represents the profile ob-
tained after incubating the plasma with 125I-glucagon. Additional clinical de-
tails in these patients are as follows: Panel 1: Healthy subject (20 yrs). Panel 2: Diabetic (19 years old; diabetes 7 yrs). Plasma glucose: fasting, 125 mg/dl; two hour post prandial, 245 mg/dl; urinary glucose excretion, 15.6
gm/24 h. Patient was in good control, with normal renal function. Panel 3:
Diabetic (58 years old; diabetes 8 yrs). Normal weight, treated with acetohex-
amide. Plasma glucose: fasting, 148 mg/dl; two hour post prandial, 340 mg/dl.
Urinary glucose excretion, 88 gm/24 h. Diabetic control poor. Normal renal func-
tion. Panel 4: Seventy-one year old obese female, previously unrecognized to be
diabetic. Presented in coma; plasma glucose, 1080 mg/dl; plasma ketones, trace.
Panel 5: Twenty-two year old female, previously well, with no history of diabetes.
Presented in diabetic ketoacidosis; plasma glucose, 720 mg/dl. Panel 6: Twenty-
two year old male, diabetic since the age of five, control generally poor, retino-
pathy with blindness, nephropathy with chronic renal failure (creatinine 2.7
mg/dl). Panel 7: Fifty-eight year old female. Presented with one month history
of necrolytic skin rash, stomatitis and 10 pound weight loss: multiple hepatic
tumor nodules identified as A cells on biopsy. Probable tumor blush in the tail
of pancreas on angiography. Blood glucose: fasting, 180; one hour, 412; two
hours, 342 mg/dl.