Another example is growth hormone (GH), for which a specific high-affinity binding protein homologous with the extra cellular domain of the growth hormone receptor is present in human plasma (71,72). At least two GH-binding proteins (GHBP) have been identified in plasma with respectively high and low binding affinities for GH (64). Growth hormone binding protein binds about 40–50% of circulating GH at low GH concentrations of about 5 ng/mL (73). At higher circulating GH levels, the binding proteins become saturated (Fig. 11). The clearance of bound GH is about 10-fold slower than that of free GH (74). Consequently, the binding proteins prolong the elimination half-life of GH, and as a result, enhance or prolong its activity. On the other hand, plasma binding of GH prevents access of free GH to its receptors, and this could decrease its activity (64).

Other protein therapeutics seem to bind to circulating proteins in a more nonspecific way. As an example, a recombinant derivative of hG-CSF, nartograstim, showed 92% binding in rat plasma, presumably to albumin (35).

6. INTERSPECIES SCALING

Techniques for the prediction of pharmacokinetic parameters in one species from data derived from other species have been applied for many years (75,76). Such scaling techniques use various allometric equations based on body weight (see Chapter 2). The following allometric equation is routinely employed:

$$P = a.W^b$$

where P is the pharmacokinetic parameter being scaled, W is the body weight, a is the allometric coefficient, and b is the allometric exponent. Although a and b are specific constants for any compound and for each pharmacokinetic parameter, the exponent b seems to average around 1 for volume terms such as the volume of distribution and 0.75 for rates such as elimination and distribution clearances. Since the elimination half-life of any drug is proportional to the volume of distribution and inversely proportional to the elimination clearance, b is about 0.25 for elimination half-lives. Allometric scaling of pharmacokinetic parameters has been difficult for small synthetic drug molecules, especially for those drugs with a high hepatic clearance and quantitative and/or qualitative interspecies differences in metabolism. In contrast, the biochemical and physiological processes that are responsible for the pharmacokinetic fate of biologics such as peptides and proteins are better conserved across mammalian species. As such, allometric scaling for those compounds has been more reliable and accurate (77). It is our experience that the systemic exposure in humans of proteins that follow linear pharmacokinetics can be predicted within a factor of two from pharmacokinetic data from 3 to 4 animal species. As a typical example, we could