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Drug Binding to Human Alpha-1-acid Glycoprotein in Health and Disease

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I. Introduction

THE PLASMA binding of drugs can have important pharmacokinetic implications, especially when the drugs are highly bound having a binding constant larger than approximately 10^5 M^{-1} and when their apparent volume of distribution is small (61, 136, 186, 266, 270, 307, 318, 347, 383, 391, 406, 446, 493, 497–499, 527, 537, 538, 573, 587).

Human serum albumin (HSA)† and alpha-1-acid glycoprotein (AGP) are the important drug binding proteins in plasma. HSA is the most abundant protein (4 g/100 ml of plasma), whereas the normal AGP level varies between about 50 and 100 mg/100 ml of plasma. The AGP level can vary considerably as a result of certain diseases, the use of drugs, and pregnancy. Values of up to 300 mg/100 ml of plasma have been found (396, 406, 426, 513, 538; see also table 6). HSA is largely responsible for the plasma binding of acidic drugs, whereas AGP binds mainly basic and neutral drugs. Although HSA has a greater binding capacity than AGP, especially for basic and neutral drugs, AGP can be the most important determinant in plasma binding, due to its greater drug affinity (44, 55, 75, 82, 83, 136, 194, 261, 358, 376, 385, 396, 450, 540, 544; see also table 8).

Drug monitoring is of increasing importance in clinical practice, especially in the case of drugs with a small therapeutic index. If such drugs are highly bound in the plasma and have a small volume of distribution, the free concentration of the drug in plasma will be a more reliable parameter for representing the intensity of the pharmacological effect than the total plasma concentration (3, 49, 71, 72, 79, 88, 189, 192, 202, 270, 277, 278, 308, 310, 321, 347, 395, 406, 408, 445, 518, 528, 538, 546, 556). If variations in the plasma levels of AGP occur, then the free plasma level of the drugs in question can vary considerably, whereas the total drug concentration of the drug in plasma will be only slightly affected (49, 108, 192, 210, 277, 278, 347).

A thorough review of the studies on the binding of drugs with AGP, both in vitro and in vivo, has been made in order to obtain a better understanding of the different factors which can affect the free plasma level of such drugs. These factors include the effects of exog-

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† Abbreviations used are: AGP, alpha-1-acid glycoprotein; B, bound fraction of a drug; B/F, binding ratio of a drug; c_{bound}, bound concentration of a drug; c_{free}, free concentration of a drug; F, free fraction of a drug; F_{AGP}, free fraction of a drug in an AGP solution; F_{HSA}, free fraction of a drug in an HSA solution; $F_{AGP+HSA}$, free fraction of a drug in a solution of a mixture of AGP and HSA; HSA, human serum albumin; K_{AGP}, drug-AGP binding constant; K_{HSA}, drug-HSA binding constant; LIPO, lipoprotein(s); n_{AGP}, number of binding sites on AGP; n_{HSA}, number of binding sites on HSA; P, plasma protein concentration; P_{AGP}, plasma concentration of AGP; P_{HSA}, plasma concentration of HSA ; P_{LIPO}, plasma concentration of LIPO.

enous and endogenous substances on the binding profile of drugs to AGP, the in vitro to in vivo correlations of free level determination, and the reliability of the free level determination. We have also studied what precautions should be taken in order to upgrade the reliability of the determination of the free concentration, and we have examined the role the physical-chemical properties of isolated samples of AGP play in results of in vitro binding studies. The binding of several therapeutic classes of drugs to AGP is reviewed. The value of the use of AGP as a diagnostic and prognostic acid in disease states is reviewed as well.

II. Isolation, Structure, and Physical-Chemical Properties of Alpha-1-acid Glycoprotein

AGP, also called orosomucoid, has been a subject of study for more than 90 yr (257, 258, 396, 469). In table 1, a survey of these studies on AGP is given.

The isolation, the structure, and the physical-chemical properties of AGP have been reviewed earlier (257, 258, 469, 578). From these review studies it has become clear that there are several forms of AGP which differ in their structure and physical chemical properties. These forms have been described in terms of their physical-chemical properties (table 2).

Native AGP, asialo or desialylated AGP, modified AGP, and abnormal AGP are heterogeneous forms of AGP which differ in their molecular weight and/or electrophoretic pattern (tables 3 and 4). The molecular weight of native AGP, modified AGP, and abnormal AGP is about the same, whereas that of desialylated or asialo-AGP is lower (table 3). The amount of polymer that forms in native AGP during isolation determines the molecular weight of the polymers of AGP. The several heterogeneous forms of AGP have electrophoretic patterns which differ in the number of bands, in the moving velocities of these bands, and in the intensities of these bands, because of small charge differences in the peptide chain and carbohydrate moiety of AGP (table 4). AGP samples with different electrophoretic patterns are generally reported as different microheterogeneous types of AGP or simply as the occurring polymorphism of AGP (469). In the literature the names of heterogeneous forms or variants of AGP are sometimes, incorrectly, used to denote microheterogeneous types of AGP (469).

In this section the physical-chemical properties of several variants of AGP, such as molecular weight, stability, and microheterogeneity, will be reviewed.

A. Methods for Isolating Alpha-1-acid Glycoprotein

Many studies dealing with methods for isolating AGP have been reported (54, 94, 98, 119, 173, 213, 219, 257, 258, 297, 298, 306, 319, 320, 334, 388, 469, 484, 560, 570, 579, 593, 594). All the procedures described are time consuming due to the use of a series of sequential chromatographic and/or precipitation steps. Recently two- and three-step purification methods, starting from Cohn Fraction VI, have been reported (217, 303, 505). Succari et al. (515) reported recently on a two-step purification method starting from plasma itself. Because in this procedure exposure to strongly acidic conditions was prevented, the investigators could obtain an AGP sample which had not undergone desialylation. Hellerstein et al. (225) recently described a time-saving isolation method

TABLE 1
Survey of the history of the studies on AGP

No.	Subject	Period	Ref.
I	Isolation and characterization	From 1882 until about the 1960s;	54, 98, 173, 257, 258, 297, 298, 334, 466, 468, 469, 476, 484, 485, 512, 560, 570, 579, 593, 594
		again from the end of the 1970s, due to the observation that the physical-chemical properties of AGP are dependent on the isolation procedures used	12, 23, 97, 102, 123, 217, 225, 303, 515; section II
II	AGP as acute phase protein	The 1960s and the 1970s	129, 137, 152, 196, 199, 293, 446; section III
III	AGP as drug carrier for steroids	The 1960s	181, 182, 565
IV	AGP as acute phase protein and as diagnostic and prognostic aid during therapy of several disease states	Since the 1980s	164, 165, 178, 184, 221, 472, 553; section III A
V	AGP as drug carrier, especially for basic drugs; as drug carrier for some acidic drugs	Since the 1980s	396, 412, 460 249, 544, 545; section IV

TABLE 2

Surveys of the several names and variants of AGP

Survey of the several names used for AGP

No.	Name	Origin name	Period used	Ref.
I	*Tierisches Gummi*	Carbohydrate substance, isolated from blood, with properties identical to those of Tiergummi (297), a mucoid isolated from snails	Sporadically, 1892	173, 297, 431
II	Seromucoid	Mucoid isolated from serum with properties comparable to those of ovomucoid, a mucoid isolated from eggs [ovum (Latin) = egg]	Always until about 1960, later sporadically	27, 173, 221, 257, 258, 273, 431, 548, 578, 593, 594
III	Alpha-1-acid glycoprotein	Acid plasma protein classified as an alpha-1-globulin and with a low isoelectric point (3.4) and a molecular weight of about 40,000	Since 1942 the name most often used	334, 475, and most refs. of table 6
IV	Mucoprotein	Glycoprotein with 30% to 50% carbohydrates	Very sporadically, about 1950	500, 560, 578, 579
V	Orosomucoid	Mucoid isolated from serum, with a high solubility in boiling water (98); [oros (Greek) = aqueous part of blood]	Since 1950 often used	53, 56, 57, 70, 93, 98, 199, 208, 211–213, 274, 302, 488, 560, 570
VI	Alpha-1-glycoprotein of Schultze	Alpha-1-glycoprotein with a molecular weight of about 54,000, first described by Schultze et al. (484)	Very sporadically, 1955, 1962	152, 484

No.	Species	Defined as	Ref.
I	Native AGP	Isolated from plasma or serum, and probably with the same properties as in vivo	53, 102, 107, 179, 213, 267, 268, 311, 371, 372, 388, 499, 500, 582
II	Delipidated or defatted AGP	AGP with a lower content of fatty acids than native AGP, resulting from ethanolic or charcoal treatment	97, 107, 181, 211, 212, 213, 282, 285
III	Asiolo- or desialylated AGP	Native AGP from which essentially all sialic acid groups of the carbohydrate groups are removed enzymatically; but sometimes called modified AGP	20, 21, 50, 53, 73, 74, 102, 124, 177, 211, 268, 356, 421, 494, 499, 582
IV	Modified AGP	Native AGP from which amino acid groups of the peptide chains are modified; also sometimes used for asialo-AGP	53, 181, 259, 294, 335, 419, 489, 490, 499, 555
V	Abnormal AGP	Native AGP, isolated from serum or plasma of patients, with physical-chemical properties different from native AGP isolated from serum of healthy people	73, 74, 104, 140, 162, 215, 250, 323, 392, 448, 489, 490, 595–598
VI	Polymers of AGP	Polymers of native AGP formed during its isolation and/or purification; degree of polymerization depends on the procedures used	35, 212, 508, 569, 571
VII	Microheterogeneous types of AGP = polymorphism of AGP	Variants or heterogeneous forms of AGP (this table, nos. I–VI) with differences in their electrophoretic patterns (different number of bands, different velocity of these bands, and/or different intensity of these bands)	14, 15, 489, 490, 494, 529. see also refs. to table 4

TABLE 3
Survey of reported molecular weights for AGP

No.	Method used	Remarks on the AGP preparation used	Values	Ref.
I	Diffusion-viscosity	Native AGP, isolated according to Weimer et al. (560)	44,100	500
II	Light scattering	Two different forms of AGP, referred to as "alpha$_1$-niedermolekulares Säureprotein" and "alpha$_1$-Glykoprotein (3.5)" or "alpha$_1$-acid glycoprotein of Schultze," respectively, isolated by using precipitation	40,000	152, 483, 484
			54,000	152, 483, 484
	Adsorption methods			
III	Sedimentation-diffusion	Native AGP, isolated from Cohn fraction VI by chromatography on carboxymethyl cellulose	41,600	53
	Sedimentation-viscosity	Same method	43,000	53
	Sedimentation-diffusion	Desialylated AGP, isolated as described above	38,600	53
	Sedimentation-viscosity	Same method	41,600	53
IV	Sedimentation-diffusion	Native AGP, isolated according to Weimer et al. (560)	37,700	267
	Sedimentation-viscosity	Native AGP, isolated according to Weimer et al. (560)	36,700	267
	Light scattering	Native AGP, isolated according to Weimer et al. (560)	48,000	267
V	Sodium dodecyl sulfate-polyacrylamide gel electrophoresis	Native AGP, isolated by electrofocusing	40,000	311
VI	Osmotic pressure, sedimentation equilibrium	Native AGP, isolated according to Buergi and Schmid (94)	41,100	268
			39,000	268
	Osmotic pressure, sedimentation equilibrium	Desialylated AGP, isolated as above	34,600	268
			34,100	268
VII	Sedimentation-diffusion	Native AGP, isolated from plasma using several ion exchange chromatography methods	44,680	388
VIII	Polyacrylamide slab gel electrophoresis	Two forms of AGP, one isolated from urine, the other from lymphocytes, granulocytes, and monocytes membranes	41,000	180
			52,000	180
IX	Exclusion chromatography on Sephadex G-200	Two forms of AGP with common immunological determinants and almost identical amino acid composition but different amounts of carbohydrate, isolated from liver metastases of several tumors	45,000	104
			37,000	104
X	Not mentioned	Isolated by Behringwerke	44,100	100
XI	Polyacrylamide gel electrophoresis	Native AGP, isolated according to Gangula et al. (182); total carbohydrate content about 47%	45,000	371, 372
XII	Polyacrylamide slab gel electrophoresis	Native AGP, isolated according to Laurell et al. (300) followed by a purification using hydroxyapatite high-pressure liquid chromatography	48,000	179

which is suitable for large numbers of small-volume samples of plasma. They pointed out that it was important to check for the possible occurrence of desialylation during the acid precipitations. Halsall et al. (213) described an isolation method for native AGP from nephrotic urine under practically physiological experimental conditions. Arnaud et al. (23) described a preparative isoelectric focusing procedure starting from albumin-depleted serum, which resulted in the separation of at least seven microheterogeneous types of AGP (section II D).

On studying the literature dealing with AGP, one notices that the stability, denaturation, and polymerization of AGP are hardly discussed at all in clinical, phar-

TABLE 4
Results of reported microheterogeneous studies of AGP

No.	AGP used and method used	Results	Ref.
I	Neuraminidase-treated AGP; starch-gel electrophoresis, pH 4.8	Three types, each having two bands: Type I Slower moving main band and faster moving minor band Type II Faster moving main band and slower moving minor band Type III Two main bands at same position as main bands of types I and II	535
	Native AGP; starch-gel electrophoresis, pH 2.9	Three types with 7, 6, and 7 bands, respectively, and corresponding to the types I, II, and III, respectively, but after neuraminidase treatment of these three native types	535
II	Native AGP; starch-gel electrophoresis, pH 2.9	Four types with 5, 6, 7, and 8 bands, respectively, occurring at a relative incidence of 4, 36, 49, and 11%, respectively, and probably due to genetically determined types	470
III	Neuraminidase-treated AGP; starch-gel electrophoresis, pH 5.1	Three types, each with two bands; relative percentages of these three types differ between a white and a Japanese population; types genetically determined; different types due to differences in polypeptide moiety	478
IV	Neuraminidase-treated AGP; starch-gel electrophoresis, pH 5	Three types, each with two bands; types independent of stress (after surgery, during pregnancy, and after delivery), and genetically determined	534
V	Neuraminidase-treated AGP from plasma of patients with uterectomy and irradiation; starch-gel electrophoresis, pH 5	Three types, each with two bands; types independent of disease and AGP plasma level; types genetically determined	591
VI	Neuraminidase-treated whole serum; agarose-gel electrophoresis, pH 5, and immunofixation	Three types, each with two bands, called SS, FE, and FS, corresponding with types I, II, and III, respectively; types genetically determined; types due to differences of amino acid composition of the peptide chain resulting in F and S bands with different electrophoretic mobilities	263
VII	Native AGP; isoelectric focusing	Two types with a relatively anodic and cathodic distribution of 6 to 8 bands, respectively; isoelectric points range from 2.90 to 3.30	52
	Neuraminidase-treated AGP; isoelectric focusing	Two types with one or two main bands, both exhibiting several minor components; isoelectric points, 4.55 and 4.70, respectively; pattern not correlated with those of native AGP; microheterogeneity due to amino acid replacements of polypeptide chain in combination with different linkages of sialic acid to carbohydrate residues in native AGP	52
VIII	Native AGP; isoelectric focusing and titration curves	At least seven bands with isoelectric points between 3.4 and 3.8; microheterogeneity very slight, between pH 6 and 8	23
	Neuraminidase-treated AGP; isoelectric focusing and titration curves	The same pattern as for native AGP, but with isoelectric points between 4.3 and 4.7; very slight microheterogeneity, between pH 6 and 8; microheterogeneity not due to differences in sialylation, but to other mechanisms	23

TABLE 4—Continued

No.	AGP used and method used	Results	Ref.
IX	Whole plasma of depressive patients; isoelectric focusing	Three types with 6, 7, and 8 bands, respectively, independent of total AGP level; isoelectric points range from 3.2 to 3.9; types due to genetically determined variants	530
X	Sera of cancer patients; crossed-immunoaffinity electrophoresis; binding to wheat germ agglutinin	Distribution of three bands changed in cancer disease; lower binding in cancer disease to wheat germ agglutinin possibly due to diminished content of sialic acids in outer part of carbohydrate moiety	65
XI	Crossed-immunoaffinity electrophoresis; influence of estrogen level	Pattern with three bands, changing to a pattern with two bands with more of the concanavalin A nonreactive bands after increase of sex hormone levels (during pregnancy and after estrogen therapy of prostatic cancer)	563
XII	Sera of healthy people, of cancer patients, and of women during pregnancy; crossed-immunoaffinity electrophoresis	Three bands in serum of normal subjects, but only two bands in serum of women during pregnancy and in serum of prostatic cancer patients treated with estrogen; increase of faster moving bands and disappearance of concanavalin A reactive band	427
XIII	Normal and inflammatory sera; crossed-immunoaffinity electrophoresis	Three bands with differences in pattern of distribution between normal and inflammatory sera; increase of concavalin A reactive and concanavalin A weakly reactive bands during inflammation	373
	Concanavalin A affinity chromatography followed by isoelectric focusing	Only two bands, when separated by chromatography, namely a concanavalin A nonreactive band, which after isoelectrofocusing had 6 bands between pH 2.9 and 3.1 and 3 bands between pH 3.1 and 3.4, and a concanavalin A reactive band with 6 bands between pH 3.1 and 3.4 when followed by isoelectric focusing	374
	Concanavalin A affinity chromatography followed by crossed-immunoaffinity electrophoresis	Only two bands, when separated by chromatography; the concanavalin A nonreactive bands separated chromatographically contain, when followed by crossed-immunoaffinity electrophoresis, the nonreactive and the weakly reactive bands, whereas the A reactive component separated chromatographically contained, after crossed-immunoaffinity electrophoresis, a little weakly reactive band too; this band is also present in sera after crossed-immunoaffinity electrophoresis alone	374
XIV	AGP from sera of normals and patients with neoplastic disease; crossed-immunoaffinity electrophoresis followed by isoelectric focusing	In neoplastic disease additional bands between pH 3.7 and 4.4, compared with normals having bands between pH 3.2 and 3.8; due to differences in amino acid substitution and the presence of a non-covalently bound chromophoric group	598
XV	Crossed-immunoaffinity electrophoresis	Patterns with three bands, but with variable distribution of these bands; in severe disease and pregnancy these patterns change towards the less concanavalin A binding bands due to changes in the glycosylation of carbohydrate moiety of AGP, depending on severity of disease state	68, 69
XVI	Crossed-immunoaffinity electrophoresis	Three bands with a relative distribution of 44.5%, 40.4%, and 16.1%, respectively, being constant under nonpathological conditions	237

TABLE 4—Continued

No.	AGP used and method used	Results	Ref.
XVII	Crossed-immunoaffinity electrophoresis	Four bands being differently distributed in normal health, inflammatory lung disease, and cancer of the lung; benign sera contain more of the concanavalin A nonreactive bands whereas cancer sera contain more of the concanavalin A reactive band; aid in diagnosis of cancer	214, 216

macological, or physical-chemical studies, although they are mentioned briefly in a few more fundamental physical studies (35, 97, 211–213, 274, 388, 507, 508). Presumably, most researchers assume that AGP is a very stable plasma protein. However, it should be noted that a temperature-dependent polymerization of AGP has been described, yielding two kinds of polymers differing in their biological activity (35) and in their drug-binding behavior (508). Halsall and Kirley (211) observed a temperature-dependent denaturation of AGP which is influenced by the degree of defatting and desialylation. From these observations, it can be concluded that sterilization of AGP by heating can induce denaturation of AGP.

Halsall et al. (212) reported (*a*) that aggregates of AGP are formed as a result of lyophilization or ultrafiltration; (*b*) that the acid-charcoal defatting procedure of Chen (109) induced polymer formation of AGP; (*c*) that lyophilization, especially of defatted AGP, induced polymerization, whereas the extent of polymerization proved to be dependent on the medium, the number of lyophylization cycles, and the protein concentration (increasing polymerization with decreasing protein concentration). They suggested therefore that care must be taken with defatted AGP and that lyophilization must be performed after extensive dialysis of an aqueous solution. Halsall et al. (212) observed further that AGP could be stored for 1 wk at 4°C in phosphate-buffered saline solution without the occurrence of polymerization, and that repeated freezing of an AGP solution and subsequent thawing did not result in polymerization. Recently, Busby and Ingham (97) reported that the thermal stability of AGP (as determined with fluorescent probes) is enhanced by lipids, propranolol, ethanol, and probably other organic solvents.

These studies demonstrate that different isolation and purification procedures result in AGP preparations with different physical-chemical properties.

B. Molecular Weight of Alpha-1-acid Glycoprotein

The molecular weights reported for AGP (see table 3) range from 37,000 to 54,000. These values depend on the methods of determination (53, 268), on the isolation procedure (97, 104, 152, 180, 205, 484), on whether the AGP is native or desialylated (e.g., as a result of neuraminidase treatment; 53, 268), and on the origin of the AGP samples (from plasma, urine, or membranes of normals or patients; 104, 180, 213, 215, 323).

The molecular weight generally assumed for AGP is 40,000, which is about the mean value of the molecular weights reported for native AGP isolated from plasma (reported values, 38,800 to 48,000; table 3). Higher molecular weights for AGP have been reported by Schultze et al. (484; table 3, no. II), Easton et al. (152), Hardwick and de Vaux St. Cyr (219), and Gahmberg and Andersson (180; table 3, no. VIII). Gahmberg and Andersson (180; table 3, no. VIII) reported, however, that the AGP with a molecular weight of 52,000 was a membrane-bound form of AGP, synthesized by the lymphocytes, but subsequently cleaved and released as the soluble serum form of AGP with a molecular weight of 41,000. Hardwick and de Vaux St. Cyr (219) and Easton et al. (152) reported the isolation from urine and serum of two AGP variants, with a molecular weight of 40,000 and 54,000, respectively. From table 3 it follows that desialylated AGP has a mean molecular weight of about 38,000 (reported values between 34,100 and 41,600; table 3).

Recently the amino acid sequence of human AGP has been inferred from the cDNA sequence using the molecular cloning technique (64). The molecular weight of the polypeptide moiety studied can be easily calculated from this sequence. Board et al. (64) remarked, however, that clones with different sequences can not yet be excluded. In order to find the total molecular weight of human AGP, the molecular weight of the five glycan chains should be added to that of the polypeptide chain.

C. Structural and Physical-Chemical Properties of the Polypeptide and Carbohydrate Moiety of Alpha-1-acid Glycoprotein

The chemical properties of AGP have been reviewed by Jeanloz (256, 257) and Schmid (469). AGP contains carbohydrate residues chemically bound to the protein. Therefore it can be catalogued among the groups of the glycoproteins (279, 487, 512), the mucoproteins (512, 560), the seroglobulins (298), and the alpha-1-globulins (265, 484).

AGP is composed of a single polypeptide chain and five carbohydrate moieties. Recently it has been shown that the polypeptide chain consists of 183 amino acids (64) [in contrast to the number of 181 reported earlier (469)] and contains two disulfide bonds (469, 471). The complete amino acid sequence, the multiple amino acid substitutions (21 of the 181 residues), and the homology with the immunoglobulins (about 80%) have been re-

ported by Schmid et al. (474, 475). Recently the amino acid sequence of the polypeptide chain of AGP was deduced from the cDNA nucleotide sequence (64). There was an excellent agreement with the amino acid sequence reported earlier by Schmid et al. (475). There was only a difference at four places on the polypeptide chain (64, 469, 475).

The five carbohydrate moieties of AGP are located in the first half of the peptide chain and are linked to asparagine residues. The carbohydrate moieties consist of about 11% sialic acid, 14% neutral hexoses, 14% hexosamine, and 1% fructose (512). It should be pointed out here that human plasma proteins contain only N-acetylneuraminic acid, whereas proteins of other species may have variable proportions of the N-acetyl and N-glycosyl derivatives (382, 512, 577). The sialic acid residues, being easily removable (224), may be linked to C-2, C-3, C-4, or C-6 of the galactose residues (258, 469). The unusually low isoionic point of 3.4 is caused by the high sialic acid content (257, 469, 557). The literature up to 1972 dealing with the chemical identification of each of the five different carbohydrate moieties of AGP is reviewed by Jeanloz (257). The structure of the carbohydrate moiety of AGP has been studied extensively in recent years (25, 167, 224, 296, 477, 486, 487, 590). Fournet et al. (167) determined the primary structures of 16 asialo carbohydrate units derived from AGP, using 360 MHz proton nuclear magnetic resonance (NMR) spectroscopy. The asialocarbohydrate units can be grouped in five classes with bi-, tri-, and tetraantennary structures, respectively, for the first three classes. The fourth and fifth classes have also a tri- or a tetraantennary structure, but with an additional fucose residue. In addition to the five chains reported by Fournet et al. (167), Yoshima et al. (590) elucidated the structure of three new sugar chains. Hansen et al. (215) reported recently significant differences in antennary structure of the glycan part of AGP from different patient groups.

Recently, Cardon et al. (102) succeeded in analyzing the sialyloligosaccharides of AGP by high-performance liquid chromatography. They found that native AGP contains no traces of neutral oligosaccharides, but only monosialylated (5.8%), disialylated (34.6%), trisialylated (43.3%), and tetrasialylated (16.2%) glycans.

Crystals of AGP have been described (344, 345, 467). However, a detailed three-dimensional structure as determined from X-ray crystallography has not yet been reported. Schmid et al. (473) studied the tertiary structure of AGP in solution using circular dichroism (259) and chemical modification methods.

Aubert and Loucheux-Lefebvre (25) reported that the protein moiety of AGP contains 21% alpha-helix, 21% beta-sheet, 8 reverse beta-turns, and 40% unordered structure. They observed that, of the five carbohydrate moieties, four are linked to asparagine residues which are situated either in a reverse beta-turn or in regions where charged and polar residues are numerous, that is, on the outside of the protein. They also reported that the carbohydrate moieties do not produce any perturbation of the protein conformation. Schmid et al. (472) reported that, even after removal of 85% of the carbohydrate content, the secondary structure of the AGP was not affected.

Several studies show that the physical-chemical properties of AGP can change during disease states. Recently, Chandrasekaran et al. (104) isolated from liver metastases of lung, colon, and breast tumors two variants of AGP with common immunological determinants and almost identical amino acid compositions but different amounts of carbohydrate. Rudman et al. (448) found an abnormal AGP in the plasma of patients with neoplastic disease. This abnormal AGP had a molecular weight of between 40,000 and 50,000, a normal protein moiety, but multiple abnormalities in the carbohydrate moiety. An AGP variant in the plasma of cancer patients has been reported (162, 595–598). This abnormal AGP contains a chromophoric group which has the characteristics of a pteridine. It has a less negative charge, although its sialic acid content is not reduced. It exists partially in a polymeric form, possibly due to the cross-linking effect of the chromophoric group. Its extinction values and optical rotary dispersion (ORD) data indicate differences in the secondary structure. Ziegler et al. (596, 597) reported recently that the decreased negative charge of this AGP (595) is due to the binding of the pteridine chromophore to the sialic acid antennae. Serbource-Goguel et al. (489, 490) reported the presence of partially desialylated AGP in plasma from patients with liver disease. The degree of desialylation of AGP was dependent on the severity of the liver disease.

D. Microheterogeneity of Alpha-1-acid Glycoprotein

The several heterogeneous forms or variants of AGP (table 2) can have different electrophoretic patterns. This phenomenon is called the microheterogeneity of AGP.

The results of the studies on the microheterogeneity of the variants of AGP are summarized in table 4. From this table it follows that the microheterogeneity is dependent on the state of AGP (native or asialo), the characterization technique used, and the origin of the AGP preparation (from normal volunteers or patients; 14, 62, 73, 74). Umetsu et al. (543) introduced recently a new technique for isoelectric focusing, which is not included in table 4. Hanssen et al. (215) reported recently that the electrophoretic microheterogeneity of AGP can be evaluated in terms of the antennary structure of the glycan part of AGP and that significant differences in glycan structure were found in different patient groups. Serbource-Goguel et al. (489, 490) reported recently about the alterations in relative proportions of microheterogeneous forms of AGP in liver disease. Mackiewicz et al. (323) observed that the microheterogeneous forms can be used as indicators of rheumatoid arthritis activity.

Charge differences in the polypeptide and carbohy-

drate chains and structural differences in the carbohydrate moiety of AGP also play a role in the observed microheterogeneity: differences in the polypeptide chain are determined genetically, whereas differences in the carbohydrate moiety are dependent on the severity of the disease (table 4).

Tinguely et al. (529) reported that the S-variant (see table 4, no. VI) of AGP has a somewhat stronger affinity for amitriptyline and nortriptyline (table 8, nos. XXXII and III). Up till now, no other studies have been reported on the effect of the microheterogeneity of AGP on the pharmacokinetics of the drug binding (15).

III. Biological Functions of Alpha-1-acid Glycoprotein

A. Alpha-1-acid Glycoprotein as Acute Phase Protein

Since the sixties it has become clear that AGP is a plasma protein, the level of which can vary considerably during several physiological and pathological conditions. Tables 5 and 6 give a survey of these conditions. The variations in the AGP level proved to be dependent on the severity of the disease states. Whereas for healthy people plasma levels of AGP are reported to range between about 40 and 110 mg/100 ml, AGP values of up to about 300 mg/100 ml have been found during diseases (396, 406, 426, 513, 538). In order to substantiate these conclusions, data were collected from the literature. Table 6 gives a survey of quantitative data on AGP and HSA levels in the plasma of healthy people and of patients with various diseases.

From the data in table 6, it follows that the normal value of the average HSA concentration in plasma of about 4 g/100 ml can decrease until about 2 g/100 ml during disease. It further follows that the normal average plasma levels of AGP are between 50 and 100 mg/100 ml; 65% of the normal cases have a level between 60 and 80 mg/100 ml; the average value is 73 mg/100 ml. The table also gives data concerning the increase in AGP concentration in acute phase situations. About 50% of the data represent a situation in which the average value in the acute phase is twice as high as the average value in the normal situation. About 35% of the data give values that are 3 times as high. It can therefore be concluded that both AGP and HSA can be classified among the acute phase proteins (12, 293) and that especially the level of AGP in plasma can be used as diagnostic and prognostic aid during the treatment of several diseases (12, 164, 165, 178, 184, 216, 218, 221, 333, 351, 392, 423, 434, 496, 533, 541, 553, 554, 562, 595). In this study, only the acute phase behavior of AGP will be discussed extensively. The observed increased AGP level and decreased HSA level are also important in relation to drug binding; this will be discussed in section IV.

Other reports are known in which the AGP concentration was measured as a function of time (10, 80, 105, 106, 114, 122, 129, 133, 137, 152, 188, 196, 198, 199, 216, 218, 240, 260, 288, 323, 446, 454, 525, 562, 586). Monitoring

TABLE 5

Survey of several disease states and physiological conditions with varying AGP levels in human plasma

No.	Pathological/physiological condition	Ref.
I	Acidosis	140, 343
II	Age	5, 6, 16, 59, 60, 70, 77, 134, 139, 201, 242, 287, 290, 391, 397, 398; table 6, nos. III-VII, L, LI
III	Alcohol use	16, 26, 190, 452
IV	Allergy	103, 295, 393
V	(Ventricular) arrhythmia	10a, 161
VI	Arthritis	1, 42–44, 139, 288, 323, 409, 479–481, 524
VII	Bacterial infection in neonatal period	13, 56, 57, 70, 183, 454, 455; table 6, nos. VIII–XII
VIII	Burn	63, 332; table 6, nos. XIV, XV
IX	Cancer (breast, colorectal, lung, ovaries)	7–9, 76, 110–112, 114, 116, 162, 164, 184, 186, 215, 221, 241, 250, 273, 392, 409, 434, 502, 523, 526, 541, 554, 559, 562; table 6, nos. XVI–XXXV
X	Chest pain	80, 169, 269, 400; table 6, no. LXXII
XI	Chronic inactive pyelonephritis	426
XII	Chronic hemodialysis patients	147, 226, 290, 391, 435, 589
XIII	Chronic pain	178; table 6, no. LXXXII
XIV	Chronic renal failure	146, 147, 435
XV	Chronic ulcerative colitis	137
XVI	Crohn's disease	152, 409, 479, 481
XVII	Depression	85, 86, 192, 193, 380, 552; table 6, nos. XLV, XLVI
XVIII	Epilepsy	304, 339, 432, 441, 531; table 6, nos. XLVII–IL
XIX	Genetic factor	16, 59, 60; table 6, no. LII
XX	Gliomas	562
XXI	Hepatitis	391, 489, 490; table 6, nos. LV, LVI
XXII	Hormonal contraceptives use	59, 81, 301, 302, 408, 585; table 6, nos. LXXX, LXXXI
XXIII	Hyperlipoproteinemia	145, 147, 226
XXIV	Hyperlipidemia	99, 153, 154
XXV	Hypertension	200
XXVI	Inflammation	62, 137, 253, 271, 409, 423, 430, 442, 479, 480–482, 488, 561; table 6, nos. LVIII, LXIII
XXVII	Liver cirrhosis	26, 36, 187, 190, 391, 409, 447, 489, 490, 493, 524; table 6, nos. XXXVIII–XLI

TABLE 5—Continued

No.	Pathological/physiological condition	Ref.
XXVIII	Liver carcinoma	114
XXIX	Multiple sclerosis	426
XXX	Myocardial infarction	10, 34, 80, 105, 106, 133, 135, 156, 161, 169, 260, 269, 400, 439, 440, 443, 447, 449, 493, 504, 553, 583; table 6, nos. LXVIII–LXXVII
XXXI	Nephrotic disease	145, 147, 391, 496, 509, 589
XXXII	Obesity	16, 47, 48; table 6, nos. LXXVIII–LXXIX
XXXIII	Pregnancy	70, 117, 128, 135, 183, 204, 218, 235, 236, 265, 357, 367, 403, 404, 427, 454, 455, 521, 585; table 6, nos. LXXXIV–XCIII
XXXIV	Renal disease	120, 123, 145, 146, 206, 270, 391, 409, 435, 447, 493, 524; table 6, nos. XCIV, XCV
XXXV	Sex	5, 47, 59, 70, 139, 152, 163, 178, 193, 287, 290, 380, 442; table 6, nos. LXXI, LXXXIX
XXXVI	Smoking	46, 59, 134, 241, 287; table 6, nos. XCVII, XCVIII
XXXVII	Stress	156, 178, 534
XXXVIII	Surgery	129, 135, 152, 163, 171, 215, 222, 240, 351, 409, 553
XXXIX	Trauma	129, 153–155; table 6, nos. IC-CVI
XL	Uremic disease	5, 145, 147, 206, 226; table 6, nos. CVII–CXI
XLI	Wound healing	198, 351

AGP levels in this way is a useful aid in clinical therapy (table 6). Most of these data are collected from cancer patients. The elevated level of AGP for these patients (but not as a function of time) has been described extensively (76, 116, 221, 241, 273, 333, 434, 502, 523, 526, 541, 554, 559, 562; table 6, nos. XVI–XXXV). Changes in the AGP level have been correlated with the response of cancer patients to chemotherapy treatment (164, 184, 221, 591).

After myocardial infarction, higher levels of AGP (Table 6, nos. LXVII–LXXVII) with peak values on days 4 to 5 have been reported (10, 260), although Voulgari et al. (553) could not detect an appreciable change in the AGP level during the first 10 days after myocardial infarction. Other reports substantiate the use of AGP levels for diagnostic and prognostic purposes in this field (80, 105, 106, 504).

Rises in the level of AGP (for survey, see table 6) have also been observed after surgery (129, 152, 163, 351, 553), in inflammation (10, 137, 351), and during infections (56, 57, 117, 199, 279, 405, 453–455, 553). Other applications have been described in patients with chronic pain (178), rheumatoid arthritis (323), hepatic diseases (114), multiple sclerosis (426), renal dysfunction (146), and during wound healing (198, 351).

AGP levels were also monitored during pregnancy (table 6, nos. LXXXIV–XCIII). A decrease depending on the stage of gestation was observed (57, 70, 196, 236, 506, 521). Levels of AGP have been reported to be higher in the first and third trimester with a decline around 24 wk gestation (218). The use of contraceptive steroids also decreases the AGP level (59, 81, 301, 302, 408, 585; table 6, nos. LXXX–LXXXI).

Lower AGP levels were observed in the serum of patients with liver cirrhosis (26, 36, 187, 190, 391, 409, 447, 489, 490, 493, 524; table 6, nos. XXXIX–XLI) and in the serum of newborns (13, 57, 70, 183, 199, 284, 404, 423, 554, 555, 585; table 6, nos. IX–XII, LXXXVII–XCIII). The occurrence of lower AGP levels in serum of newborns (more than 2 times less than the value in healthy adults) can explain the complications that occur directly after delivery in a mother using a drug therapy.

It would be interesting to discover the reasons for this changing level of AGP. Winzler and Bocci (578) reviewed the turnover of the major plasma glycoproteins. They reported that most of the circulating plasma glycoproteins, including AGP, are synthesized in the liver (51, 127, 262, 352, 355, 456, 580), probably in the form of an intrahepatic precursor (366). Weisman et al. (561) studied the turnover of AGP in man and observed an increase in synthesis in patients with inflammatory disease. Several reports in which the mechanism of the synthesis of AGP was studied using a perfused rat liver or cultures of rat hepatocytes (38, 144) point to the role of increased mRNA in this context. Diarra-Mehrpour et al. (144) recently reported that, after a high dose of 17-alpha-ethynylestradiol and after acute inflammation, rats showed an increase in the plasma concentration of AGP, due to hepatic accumulation of the AGP-mRNA. They further concluded that different mechanisms and/or pathways are probably involved in regulating the synthesis of AGP under various stimuli such as glucocorticoids. Similar conclusions were reached by other investigators (141, 291, 312, 428, 430, 547).

The homology with immunoglobulins is also stressed. Ikenaka et al. (248) reported that AGP was the first single-chain protein that was found to show sequence similarity with haptoglobin and particularly with the immunoglobulins (36% and 75%, respectively). Schmid et al. also observed the homology of AGP with the immunoglobulins (474, 475).

Toh et al. (532) reported recently that membrane AGP has some structural homologies with the β-chain of HLA-DC, with immunoglobulin, and with the epidermal

TABLE 6

Survey of AGP and HSA levels in plasma of healthy people and patients with various diseases as reported in studies dealing with acute phase proteins

No.	Disease	Disease level		Normal level		Ref.
		AGP [mg/100 ml]	HSA [g/100 ml]	AGP [mg/100 ml]	HSA [g/100 ml]	
I	Healthy people			70–110	3.9–5.5	513
			Two populations	4.7 ± 0.5		287
			105 ± 31	4.7 ± 0.3		
			64 ± 13			
II	Atherosclerosis	115 ± 16.9 but decrease to 90 ± 24.8 after clofibrate treatment		60 ± 20		99
III	Arthritis	149 ± 60	2.9 ± 0.8	66 ± 30	4.1 ± 0.8	409
IV	Arthritis	131 ± 42		63 ± 17		436
				57 ± 13 (women)		
				69 ± 19 (men)		
V	Arthritis	180 ± 80	4.01 ± 0.8	104 ± 33 (age dependent)	4.3 ± 0.7	139
VI	Arthritis	213 ± 42		64 ± 16		427
VII	Arthritis	40 ± 20		25 ± 5		185
VIII	Bacterial infection in neonates	Increase from 32–67 on day 3		32		13
IX	Bacterial infection in neonates	Increase to about 150 ± 50, whereas during viral or parasite infection, increase to about 100 ± 50 only		Increase from 17 ± 3 at birth to 50 ± 10 at day 6		57
X	Bacterial infections in neonates	Increase to 150		Increase from 8 ± 4 at birth to 27 ± 4 after 7 days		199
XI	Bacterial infections in neonates	133 ± 75 for neonates with favorable outcome, but 167 ± 67 for neonates with poor clinical outcome		Increase from 18 ± 8 at birth to 52 ± 8 after 2 days		454
XII	Bacterial infections in neonates	Increase to about 140		30 ± 25 at birth and on day 4 about 50 ± 25		70
XIII	Bronchitis	30 ± 10		25 ± 5		185
XIV	Burn	Increase to 222	Decrease to 2.2	83	4.4	63
XV	Burn injury	Increase to about 268 and 221 between days 5 and 25, respectively	Decrease to 1.9–2.7 between days 8 and 25	66 ± 30	3 ± 1	332
XVI	Cancer of lungs	217 ± 29		76 ± 5		9
XVII	Cancer of lungs, stomach, pancreas, uterus, breast	270 ± 60		99 ± 8.3		27
XVIII	Cancer of breast, colon	118 ± 72	3.47 ± 0.61	75 ± 18	3.95 ± 0.5	76
XIX	Cancer of liver	148 ± 53		70.3 ± 2.54		114
XX	Cancer of colon	Increase to 128 ± 62, depending on stage		65 ± 40		116
XXI	Ovarian cancer	Increase to 240 depending on stage and effect of therapy		76 ± 14		164
XXII	Cancer of breast	Increase to 233		76 ± 14		165
XXIII	Cancer	Increase to 54 ± 22 depending on severity		32 ± 5		185
XXIV	Active lung cancer	120 ± 36, whereas in inactive lung cancer, only 60 ± 24		60 ± 24		184
XXV	Cancer of lung	216 ± 20, but in lung inflammation, only 176 ± 24		76 ± 4		216

TABLE 6—Continued

No.	Disease	Disease level		Normal level		Ref.
		AGP [mg/100 ml]	HSA [g/100 ml]	AGP [mg/100 ml]	HSA [g/100 ml]	
XXVI	Cancer	Increase to 137 ± 20 depending on stage and effect of therapy		73 ± 13		221
XXVII	Cancer	Increase to 352 ± 163 depending on severity		92 ± 25		241
XXVIII	Cancer	134 ± 49		53 ± 11		321a
XXIX	Prostatic cancer + stilbestrol	61 ± 7		64 ± 16		427
XXX	Advanced cancer	238 ± 71		64 ± 16		427
XXXI	Cancer	255 ± 41		69 ± 8		502
XXXII	Prostatic cancer	Increase to about 126 ± 50, but 54 ± 29 during stilbestrol therapy		Decrease to about 83 ± 21		559
XXXIII	Cancer	142 ± 54	3.11 ± 0.50	78 ± 22	4.37 ± 0.41	8
XXXIV	Cancer	151 ± 53	3.08 ± 0.51	78 ± 21	4.31 ± 0.42	7
XXXV	Cancer	219 ± 62		73 ± 15		397
XXXVI	Crohn's disease	165 ± 100	3.0 ± 1.5	66 ± 30	4.1 ± 0.8	409
XXXVII	Gliomas (brain tumor)	134 ± 48		74 ± 18		462
XXXVIII	Cirrhosis	71 ± 43		70.3 ± 2.54		114
XXXIX	Cirrhosis	Decrease to about 50		About 90		564
XL	Cirrhosis	19.5 ± 7.5		67.3 ± 18.5		36
XLI	Cirrhosis	63 ± 30	2.55 ± 1.5	66 ± 30	4.1 ± 0.8	409
XLII	Liver disease	17 ± 3	3.5 ± 1	30 ± 20	4.5 ± 0.5	187
XLIII	Liver disease	20 ± 10		25 ± 5		185
XLIV	Chronic ulcerative colitis	Increase to 387 ± 68.7, depending on severity	Decrease to 2.02 ± 0.5 depending on severity	80.7 ± 14	3.7 ± 0.3	137
XLV	Psychiatric patients	107 ± 26	4.4 ± 3.7	81 ± 22	4.6 ± 2.3	86
XLVI	Depressed patients	94 ± 30		62 ± 21		101
XLVII	Epilepsy disease	75 ± 10 after carbamazepine treatment, but 55 ± 10 after carbamazepine + phenobarbital treatment		75 ± 10		89–92
XLVIII	Epilepsy disease	75 ± 40 during carbamazepine treatment, 100 ± 50 during phenytoin treatment		60 ± 35		531
IL	Epilepsy disease	104.8 ± 50		63.8 ± 20		441
L	Elderly patients with acute disease	165 ± 59		63 ± 12		398
LI	Sick elderly patients	150 ± 56		62 ± 11 (young) 73 ± 15 (elderly)		397
LII	Genetic and environmental factors			63 ± 18 (fathers) 62 ± 18 (mothers) 62 ± 18 (children)	4.43 ± 0.41 4.34 ± 0.43 4.71 ± 0.48	16
LIII	Chronic hemodialysis patients	Before hemodialysis, 117.1 ± 37.5; after hemodialysis, 148.8 ± 44.7		65.6 ± 13.1		589
LIV	Hemodialysis	60 ± 15		25 ± 5		185
LV	Hepatitis	62 ± 25		70.3 ± 2.54		114
LVI	Hepatitis	About 90		About 90		564
LVII	Hypoalbuminemia	86 ± 29		63 ± 17		436

TABLE 6—Continued

No.	Disease	Disease level		Normal level		Ref.
		AGP [mg/100 ml]	HSA [g/100 ml]	AGP [mg/100 ml]	HSA [g/100 ml]	
LVIII	Infection	143 ± 64		73 ± 15		397
LIX	Inflammation of lungs	205 ± 38		76 ± 5		9
LX	Nonspecific upper respiratory tract infection	Increase to 140 ± 12		62 ± 28		426
LXI	Chronic obstructive respiratory disease	139 ± 40		73 ± 15		397
LXII	Bacterial infection	Increase to about 280 ± 30		80 ± 30		553
LXIII	Viral infection	Increase to about 260 ± 30		80 ± 30		553
LXIV	Malaria	Increase to about 230 ± 30		80 ± 30		553
LXV	Systemic lupus erythematosis	180 ± 90	3.6 ± 0.8	103 ± 35	4.4 ± 0.7	139
LXVI	Lupus erythematosis	Increase to about 300		About 90		564
LXVII	Myocardial infarction	Increase to 175 ± 15 at day 4		79.6 ± 15.11		10
LXVIII	Myocardial infarction	Increase to 99 ± 5 on day 3	Decrease to 3.45 ± 0.11 on day 3	69 ± 4	3.7 ± 0.08	32
LXIX	Myocardial infarction	Increase to 166 ± 40 on day 3		92 ± 20		34
LXX	Myocardial infarction	Increase to 160 ± 20 on about day 5		100 ± 10		105
LXXI	Myocardial infarction	95 ± 27 (males) 84 ± 24 (females)		69 ± 15 (males) 72 ± 15 (females)		106
LXXII	Myocardial infarction	181 ± 69; however, when chest pain, only 125 ± 37		65 ± 9		169
LXXIII	Myocardial infarction	Increase to 143 ± 13		70 ± 2.4		504
LXXIV	Myocardial infarction	Increase to about 175		80 ± 30		553
LXXV	Acute myocardial infarction	Increase to 170 on day 5	Decrease to 3 on day 5	93 ± 7	3.85 ± 0.1	131
LXXVI	Acute myocardial infarction	181 ± 69; however, when chest pain, only 125 ± 37		65 ± 9		169
LXXVII	Myocardial infarction	152 ± 70		73 ± 15		397
LXXVIII	Obesity in men	124 ± 35	4.17 ± 0.27	55 ± 6	4.31 ± 0.17	47
LXXIX	Obesity	121 ± 17	4.0 ± 0.2	62.9 ± 18.8	4.2 ± 0.2	48
LXXX	Oral contraceptives use	Decrease to about 56	Decrease to about 3.2	71 ± 17	4.7 ± 0.47	196
LXXXI	Oral contraceptives use	54 ± 15	3.9 ± 0.3	77 ± 30 (men) 64 ± 30 (women)	4.3 ± 0.6 (men) 4.1 ± 0.3 (women)	408
LXXXII	Chronic pain	137 ± 8		81 ± 7		178
LXXXIII	Acute pancreatitis	220 ± 48		64 ± 16		427
LXXXIV	Pregnancy	Decrease to 51 ± 29 in 3rd trimester; however, when inflammation present, increase to about 200		62.6 ± 18.8		117
LXXXV	Pregnancy	85.1 ± 19.7	3.1 ± 0.3	107.1 ± 19.4	4.3 ± 0.3	183
LXXXVI	Pregnancy	Decrease to about 52 ± 17	Decrease to about 3.2 ± 0.4	71 ± 17	4.7 ± 0.47	196
LXXXVII	Pregnancy	52 ± 9		64 ± 16		427

TABLE 6—Continued

No.	Disease	Disease level		Normal level		Ref.
		AGP [mg/100 ml]	HSA [g/100 ml]	AGP [mg/100 ml]	HSA [g/100 ml]	
LXXXVIII	Pregnancy	In fetal serum, increase from 5 to 20 during gestation from week 15 to 40; in maternal serum, 70 ± 30	In fetal serum, increase from 1.5 to 3.5 during gestation from week 15 to 40; in maternal serum, 3 ± 0.5	25 ± 10 at birth 70 ± 30	3.5 ± 0.5 at birth 3 ± 0.5	284
LXXXIX	Pregnancy	49.7 ± 13.0 (maternal) 20.1 ± 94 (fetal)	3.56 ± 0.36 (maternal) 4.35 ± 0.40 (fetal)			367
XC	Pregnancy	15.3 ± 4.7 (fetal) 49.6 ± 6.5 (maternal)				585
XCI	Pregnancy	72.1 ± 2.7 (maternal) 31.6 ± 2.0 (fetal)				300
XCII	Pregnancy	54.5 ± 3.7	2.48 ± 0.76	66.6 ± 18.2	4.64 ± 0.71	140
XCIII	Pregnancy	In fetal serum, increase from 10 ± 5 to 30 ± 10 during gestation from week 28 to 40		30 ± 25 at birth and about 50 ± 25 on day 4		70
XCIV	Renal disease	135 ± 50	3.3 ± 1.0	66 ± 30	4.0 ± 1.0	206
XCV	Renal disease	165 ± 100 (complicated); 82 ± 40 (uncomplicated)	2.6 ± 1.5 (complicated); 3.5 ± 1.5 (uncomplicated)	66 ± 20	4.1 ± 0.8	409
XCVI	Septicemia	247 ± 45		64 ± 16		427
XCVII	Smoking	112 ± 63		92 ± 25		241
XCVIII	Smoking	84.3 ± 12.7	4.05 ± 0.29	62.8 ± 13.3	4.30 ± 0.23	46
IC	Traumatic injury	197 ± 100		70 ± 16	4.8 ± 0.4	153, 154
C	Trauma	Increase to 243 between days 10 and 14		70 ± 16		155
CI	Surgical trauma	Increase to 216 ± 35.2 on day 5	Decrease to 4.1 ± 0.3 on day 4	Preoperative, 111.5 ± 29.1	Preoperative, 4.8 ± 0.4	24
CII	Surgical trauma	200 ± 50		115 ± 25		129
CIII	Postoperative cholecystectomy	121 ± 22		64 ± 16		427
CIV	Hip replacement	Increase to about 180		80 ± 30		553
CV	Hernia repair	Increase to about 166 ± 28 on day 6, but increase to about 500 ± 100 when pneumonia as complication was diagnosed postoperatively	Decrease to about 2.59 ± 0.47 on day 6	Preoperative, 86 ± 21	3.43 ± 0.53	564
CVI	Surgical trauma	Increase to about 180		Preoperative, about 80 ± 40		163
CVII	Uremic patients	184 ± 62		Range, 62–142		226
CVIII	Chronic inactive pyelonephritis	Increase to 240 ± 40		62 ± 28		426
CIX	Nephritis	Increase to about 300		About 90		564
CX	Uremic patients	25 ± 15		25 ± 5		185
CXI	Uremic patients on hemodialysis	Before dialysis, 117.58 ± 36.65; after dialysis, 132.19 ± 37.12		98.32 ± 19.5		147
CXII	Vasculitis	30 ± 10		25 ± 5		185

growth factor receptor. Board et al. (64) reported recently, however, using the molecular cloning technique, that the homology between AGP and the epidermal growth factor receptor was poor.

Gamberg and Andersson (180) reported the presence of a membrane-bound form of AGP (with an apparent molecular weight of 52,000) on normal human lymphocytes, granulocytes, and monocytes (17–19). They demonstrated that this membrane protein is synthesized by lymphocytes and subsequently cleaved and released in the soluble serum form that has the normal molecular weight of 41,000. They concluded that this finding may

partially explain the increase in the AGP level in serum in many disorders involving leucocyte proliferations (17–19, 256, 257, 469).

There is also evidence that levels of AGP may change in the plasma of patients and several animals after treatment with defined drugs due to enzyme induction or inhibition of the AGP production (29, 33, 39, 84, 89–92, 99, 138, 301, 330, 386, 424, 425, 429, 432, 441, 531). This phenomenon has been reviewed by Greim (203). Both an increase and a decrease in the AGP level during drug therapy have been observed. Some studies with the same drug report contradictory results. Feely et al. (159) did not find an increase in the AGP level, due to hepatic enzyme induction of the AGP by rifampicin, as observed by Routledge et al. (441) and Delcroix et al. (138). Whereas Tiula and Neuvonen (531) and Olsson et al. (386) observed an increase in the AGP level after treatment with phenobarbital or carbamazepine alone, Bruguerolle et al. (89–92) observed a decrease in the AGP level only after treatment with a combination of these two drugs. Riva et al. (432) found an increase in the AGP level after carbamazepine treatment, in accord with the results of Tiula and Neuvonen (531) and Olsson et al. (386). Riva et al. (432) were the first to use serum from epileptic children and concluded that a modification of the serum AGP due to epilepsy itself cannot yet be ruled out and may be an explanation for the discrepancy in the results. Barbosa et al. (33) reported that anabolic steroids can both decrease and increase the AGP level, depending on their structures. As can be seen in table 6, nos. LXXXIV–XCIII and LXXX–LXXXI, the AGP level is decreased during pregnancy and during the use of oral contraceptives, due to the effect of estrogens. Reuss et al. (429) reported on a model that can be used to predict the AGP level during perazine therapy. Benedek et al. (46) found that smoking also raises the AGP levels, possibly due to an alteration in the serum protein chemistry or due to the accumulation of endogenous or exogenous substances (i.e., basic compounds in the smoke itself).

Many of the discrepancies in the literature dealing with changed AGP levels after drug therapies appear to be due to attempts by investigators to draw a single conclusion from studies involving different species and different dosing regimens.

B. Several Other Biological Activities of Alpha-1-acid Glycoprotein

Many other biological properties of AGP are discussed in the literature: its immunological response behavior during several pathological states (50, 57, 110–112, 115, 253, 262, 405, 589); its protective effect against neonatal sepsis (57, 405); its inhibition of platelet aggregation (20, 21, 35, 124, 280, 342, 375, 378, 503, 507, 514, 569, 571); its interaction with collagen (124, 168); its growth-promoting effect for Hela and H-6 cells (325, 326); its involvement in the T_3-T_i antigen-specific pathway of T-cell activation (511); its interaction with phospholipid membranes (110–112, 324–326, 368–372); its occurrence as carrier of a cofactor in the lipoprotein lipase reaction (509); its inhibition of phagocytosis (388, 389); its inhibition of the multiplication of malaria parasites (174, 175, 208); its interaction with vitamin B_{12} (224); its inhibition of neutrophil activation (125); its prolongation of the survival of skin homografts (361, 388); and its histamine binding capacity (103).

Bennett and Schmid (50) reported that the effectiveness of immunosuppression is enhanced for agalacto/asialo derivatives of AGP; this points to the importance of the carbohydrate moiety in the immunoregulatory function of AGP. Cheresh et al. (112) studied sera from cancer patients and found a positive correlation between the AGP level and its immunosuppressive capacity. They observed the inhibitory effect of breast cancer serum on mitogen-induced blastogenesis of normal lymphoid cells. Cheresh et al. (111) further reported that nonspecific immunosuppression is due to electrostatic forces between sialic acids groups of AGP and phospholipids; however, no change in the lipid packing is involved because the phase transition temperature did not change. Jamieson et al. (253) found that AGP is located at the inflammatory site and may be involved in some aspects of the inflammation process.

Andersen and Eika (21) reported that totally desialylated AGP lost much of its capacity as inhibitor of the platelet aggregation, whereas Costello et al. (124) observed an increase in this effect in the presence of desialylated AGP. Barclay et al. (35) and Spragg et al. (507) observed that the inhibition of the hemagglutination was dependent on the shape and the size of the AGP polymers.

Franzblau et al. (67) reported that the interaction of AGP with collagen resulted in the formation of fibrous, long spacing fibers of collagen; presumably this process is also involved in the wound healing.

Maeda et al. (325, 326) found that AGP facilitated the passage of erythrocytes through membranes. AGP increased the bilayer thickness of liposomes and decreased the membrane permeability for ions (368, 369). More recently Neitchev (370) reported that the decreased permeability of liposomes after the addition of AGP was dependent on the AGP/protein ratio and was due to the interaction of AGP and protein with lipids, which in turn led to electrostatic changes in the membrane lipid region and membrane surface. Furthermore AGP could play the role of active modifier changing the membrane selectivity (371, 372).

Friedman et al. (174, 175) found that AGP could inhibit invasion by malaria parasites. However, Gupta et al. (208) could not confirm these inhibitory effects of AGP.

Chachaj et al. (103) studied the histamine-binding properties of plasma proteins. Their results suggested that human serum contains three histamine-binding

fractions, identified as orosomucoid and two glycoproteins belonging to the α_1-globulin group. Parrot et al. (393) and Laborde et al. (295) reported earlier that serum from patients with allergic disorders showed an impaired ability to bind histamine. The increase in the binding to histamine in allergic diseases might perhaps be ascribed to an increase in AGP, as has often been reported in other inflammatory diseases, but the possible existence of such a correlation has not been studied so far.

These many diverse activities are difficult to interpret. By careful study of the papers cited it may become apparent that many of the reported activities do not occur in a regulatory fashion at physiological concentrations of AGP, and they are therefore unlikely to be functional (177, 342, 451). In view of the purpose of this review, we will not discuss these activities in detail here.

IV. Interactions of Drugs with Alpha-1-acid Glycoprotein

HSA, AGP, and lipoproteins (LIPO) are the most important plasma proteins responsible for the binding of drugs in plasma. HSA binds in particular acidic and neutral drugs, whereas AGP and LIPO bind mainly basic drugs (82, 83, 194, 195, 358, 377, 406–408, 412, 414, 415, 450, 546). Table 7 gives a survey of studies which deal with the binding of drugs to AGP. Most of these drugs are basic ones with pK values of 8 or higher, which implies that these drugs are positively charged at physiological pH. Some of the drugs, such as phenylbutazone, phenobarbital, and the anticoagulants, are acidic and may be partially or totally negatively charged at neutral pH. Some other drugs, such as the steroids, diazepam, and carbamazepine, are neutral. From more recent studies dealing with the binding of drugs to AGP, it follows that other drugs not included in table 7 have an affinity for AGP; e.g., aminopyrine (156), amoxapine (160), bupropion (160), maprotiline (160), nomifensine (160), trazodone (160), drugs with a quaternary ammonium group (498), ritodrine (204), doxazosin (160), trimazosin (160), binedalin (358, 359), amsacrine (399), apazone (544) and SKF 525 A (45).

In this section the binding of drugs to AGP will be discussed. Section IV A will deal mainly with the relation between the varying concentration of AGP and its drug binding properties. In section IV B, the binding of basic and neutral drugs to isolated AGP is reviewed. A small section (IV C) is devoted to the binding of acidic drugs to AGP. The molecular details of the drug binding to AGP will be discussed in section IV D. In section IV E, it will be demonstrated that the results of binding studies can be strongly influenced by the experimental circumstances.

A. Binding of Drugs to Alpha-1-acid Glycoprotein in Vivo

Since the end of the sixties it has become clear that AGP can function as a drug carrier for steroids (181, 182, 565). Later it was demonstrated that AGP also has high binding affinity for several basic drugs (396, 406–408) and, as has been shown recently, for some acidic drugs as well (249, 544, 545).

Variations have been observed in the binding of basic drugs in plasma (5, 396, 406–408, 538). This has been shown to be due to variations in plasma protein concentration, particularly in several disease states. Changes in the plasma protein concentrations have been reported for drug binding plasma proteins, particularly for HSA, AGP, and LIPO (406–408, 445, 538, 546). From binding studies it follows that HSA accounts mainly for the binding of acidic and neutral drugs, whereas AGP and LIPO associate more readily with basic drugs (194, 377, 406–408, 412, 414, 415, 546). It has become clear that the drug binding capacity of AGP, especially for basic drugs, can be of the same order as or even higher than that of HSA. This implies that the large variation in the AGP level in plasma observed during several physiological and pathological conditions can have a profound effect on drug concentrations in the blood. This correlation between the extent of drug binding and the AGP concentration in plasma will be discussed in the first part of this section.

It can be concluded from the literature (194, 377, 406–408, 412, 414, 415) that HSA, LIPO, and AGP are the most important plasma proteins that play a role in plasma drug binding. This means that the total drug concentration in plasma (c^{plasma}) can be given by equation 1:

$$c^{plasma} = c_{free} + c^{AGP}_{bound} + c^{HSA}_{bound} + c^{LIPO}_{bound} \qquad \text{equation 1}$$

where c_{free} is the free concentration of the drug in plasma, and c^{AGP}_{bound}, c^{HSA}_{bound}, and c^{LIPO}_{bound} represent the concentrations bound to AGP, HSA, and LIPO, respectively. If the binding of drugs to proteins can be described by Scatchard plots (196a, 349, 457), equation 2 can be used for the calculation of the drug concentrations bound to several components (c^{i}_{bound}) in plasma:

$$c^{plasma}_{bound} = \Sigma\, c^{i}_{bound} = \Sigma \frac{n_i P_i K_i c_{free}}{1 + K_i c_{free}} \qquad \text{equation 2}$$

where n_i, P_i, and K_i are the number of binding sites, the plasma protein concentration, and the affinity constant of component i in plasma, respectively. Note that, in this review, K_i is an association constant not a dissociation constant.

The use of equation 2 has been criticized in the literature (95). In the discussion that follows, it will become clear that equation 2 will apply to situations in which the average number of occupied binding sites is much less than one. In that case, there will no longer be objections to the use of this equation. Equations 1 and 2 describe the system completely. If protein concentrations, the number of binding sites, and the binding constants are known, then c_{free} can be calculated at a

TABLE 7
Survey of studies dealing with the binding to AGP

No.	Category	Drug	Ref.
I	Alpha-blocker	Nicergoline	433
II	Alpha-blocker	Prazosin	93, 136, 160, 200, 447, 542
III	Anesthetic/analgesic	Alfentanil	245, 348
IV	Analgesic	Fentanil	348
V	Analgesic/anesthetic	Ketamine	135
VI	Analgesic	Meperedine	63, 242, 367
VII	Analgesic	Methadone	7, 136, 436, 521
VIII	Analgesic	Phenylbutazon	545
IX	Anesthetic	Bupivacaine	128, 136, 140, 404, 410
X	Anesthetic	Etidocaine	136, 357, 410
XI	Anesthetic/antiarrhythmic	Lidocaine	34, 63, 71, 134, 136, 155, 159, 191, 197, 206, 250, 285, 410, 411, 439–444, 493, 585
XII	Anesthetic	Phencyclidine	31, 190, 390
XIII	Antiarrhythmic	Aprindine	22, 524
XIV	Antiarrhythmic	Disopyramide	10a, 71, 78, 79, 131, 133, 136, 186, 222, 223, 233, 244, 264, 313–317, 346, 397, 412, 414
XV	Antiarrhythmic	Quinidine	87, 88, 136, 154, 170–172, 210, 251, 376, 377, 412, 415
XVI	Antiarrhythmic	Verapamil	136, 187, 191, 269, 338, 588
XVII	Antibiotic	Erythromycin	36, 142, 420
XVIII	Anticoagulant	Acenocoumarol	545
XIX	Anticoagulant	Dipyridamole	157, 176, 177, 281, 375, 514
XX	Anticoagulant	PCR 2362, thienopyridin derivative	195
XXI	Anticoagulant	Ticlopidine	195
XXII	Anticoagulant	Warfarin	544, 545
XXIII	Antiepileptic	Carbamazepine	37, 304, 339, 340, 432, 531
XXIV	Antiepileptic	Phenytoin	45, 411, 462, 549
XXV	Antiinflammatory agent	Naproxen	408
XXVI	Beta-blocker	Alprenolol	42, 43, 75, 136, 235, 236, 408
XXVII	Beta-blocker	Metoprolol	42, 43
XXVIII	Beta-blocker	Oxprenolol	42–45, 271
XXIX	Beta-blocker	Pindolol and 8 related compounds	42, 43, 305
XXX	Beta-blocker	Propranolol	8, 11, 16, 41–48, 63, 88, 97, 160, 161, 177, 194, 238, 247, 251, 274, 282, 342, 359, 363, 394, 397, 398, 400, 409, 411, 412, 421, 443, 449, 450, 452, 480, 488, 505, 549, 551, 557, 582, 583, 585
XXXI	Beta-blocker	Timolol	42, 43
XXXII	Estrogen	Progesterone	128, 177, 181, 182, 272, 274, 294, 442, 506, 555, 565–568, 582
XXXIII	Estrogen	Cortexone Cortisol Testosterone Estradiol	182, 272
XXXIV	Neuromuscular blocker	Metocurine	585
XXXV	Neuromuscular blocker	*d*-Tubocurarine	585
XXXVI	Psychotropic	Amitriptyline	83, 85, 86, 160, 412, 413, 415, 463
XXXVII	Psychotropic	Chlorpromazine	158, 176, 282, 359, 363, 409, 463, 549, 551
XXXVIII	Psychotropic	Cyclazindol	520
XXXIX	Psychotropic	Desmethylimipramine	84, 254, 255, 551
XL	Psychotropic	Diazepam	5, 84, 134, 206, 282, 332, 442, 462, 585
XLI	Psychotropic	Doxepin	160, 552
XLII	Psychotropic	Fluphenazine	282
XLIII	Psychotropic	Haloperidol	282, 462

TABLE 7

No.	Category	Drug	Ref.
XLIV	Psychotropic	Imipramine	6, 63, 75, 160, 169, 192, 193, 254, 255, 282, 287, 288, 332, 359, 363, 364, 408, 462, 463
XLV	Psychotropic	Loxapine	282
XLVI	Psychotropic	Mianserin	491
XLVII	Psychotropic	Nortriptyline	82, 83, 160, 412
XLVIII	Psychotropic	Norzimelidine	101
IL	Psychotropic	Perazine	82, 83, 86, 136, 429, 460–463
L	Psychotropic	Perphenazine	551
LI	Psychotropic	Phenobarbital	462
LII	Psychotropic	Phenothiazine derivatives	158, 460, 461, 463, 549–551
LIII	Psychotropic	Promazine Acepromazine Protipendyl	158
LIV	Psychotropic	Thioridazine	26, 282, 380, 381
LV	Psychotropic	Thiothixene	282, 463
LVI	Psychotropic	Triazolam	290
LVII	Psychotropic	Trifluoperazine	158, 551
LVIII	Psychotropic	Zimelidine	101
LIX	Vitamin	Vitamin B_{12}	224
LX	Fluorescent probe	DAPN, derivative of propranolol 1,8-Anilinonaphtalene sulfonate	4 97, 176

given total plasma concentration. Changes in one of the components (either drug or protein) cause several equilibria to shift until a new equilibrium is reached. However, there is no simple relationship between protein concentration and drug concentration. For the in vivo situation to be discussed below, simplifications can be made which result in equations that are easier to handle. The assumption is that $K_i c_{free}$ is much smaller than one. If this holds, then equation 2 can be reduced to:

$$\Sigma c_{bound}^{i} = \Sigma n_i P_i K_i c_{free} \qquad \text{equation 3}$$

Substitution of equation 3 into equation 1 and dividing by c_{free} yield:

$$c^{plasma}/c_{free} = 1 + \Sigma n_i P_i K_i \qquad \text{equation 4}$$

Defining c_{free}/c^{plasma} as the free fraction F, and $1-F$ as the bound fraction B, then:

$$1/F = 1 + n_{AGP}P_{AGP}K_{AGP} + n_{HSA}P_{HSA}K_{HSA} + n_{LIPO}P_{LIPO}K_{LIPO} \qquad \text{equation 5}$$

$$B/F = n_{AGP}P_{AGP}K_{AGP} + n_{HSA}P_{HSA}K_{HSA} + n_{LIPO}P_{LIPO}K_{LIPO} \qquad \text{equation 6}$$

Equations 5 and 6, which are much easier to deal with than equations 1 and 2, can be used to study the influence of varying AGP concentrations on B/F or $1/F$. If the concentration of HSA and LIPO remains constant, then the binding ratio B/F varies linearly with the AGP concentration.

From the literature, data were collected on drug levels in plasma as a function of AGP concentration. Some authors had already analyzed their data according to equation 6. Others presented an analysis in which F was plotted versus the AGP concentration. However, as shown in equation 5, only for $1/F$ versus the AGP concentration could a linear relationship be expected. These relationships were replotted by us in the form of B/F and are denoted as "transformed" in table 8.

Table 8 presents a survey of those studies in which drug binding was measured as a function of AGP concentration. The drugs studied are listed in the second column. Except for prednisolone and triazolam, which are neutral, all the drugs are basic ones, and nearly all of them are positively charged at neutral pH. The next column gives the AGP range studied. The fourth column shows that the free fraction F might indeed vary strongly, and it is this variation which might have therapeutic consequences. Column 6 gives the linear correlation found between B/F (y) and the AGP concentration (x), expressed in mg/100 ml, together with the correlation coefficient r. As judged by this value of r, many good linear relationships are found, which means that the variation in F, and therefore in c_{free}, is caused by the variation in the AGP concentration. It should be noted that not all relationships reported in table 8 are significant, particularly when r becomes smaller than 0.7. Then r^2 is smaller than 0.5, which in turn means that only 50% of the total variance can be explained by the observed relationship. The variation occurring in the HSA level in disease states (table 6) may be a possible reason.

The value of $n_{AGP}K_{AGP}$ has been calculated from the slope of the relationships given in table 8 (column 7). Two compounds (VI and XXXII) show a relatively high value of $n_{AGP}K_{AGP}$. About 90% of the remaining values are found in a relatively small range between 8×10^4 M^{-1} and 8×10^5 M^{-1}. This is surprising and probably points to some common structural elements in these drugs. In addition, these values allowed us to verify that, for the most cases studied, Kc_{free} was indeed much smaller than one. Lidocaine might be an exception (285).

TABLE 8

Survey of the studies dealing with the correlation between the binding ratio and the concentration of AGP in plasma/serum for several drugs and in several disease states

No.	Drug	Disease	AGP range [mg/100 ml]	F range	B/F	$n_{AGP}K_{AGP} \times 10^{-6}$ [M^{-1}]	Ref.
I	Alprenolol	Healthy people	38–113	0.22–0.09	$y = 0.053x + 1.97$ $r = 0.72$	2.14	408, fig. 1, transformed
II	Alprenolol	Pregnancy (mother/newborn)	8–70	0.44–0.12	$y = 0.073x + 0.59$ $r = 0.72$	2.95	236, fig. 7
III	Amitriptyline	Depressive patients	17–118 (concentration of S-variant of AGP)	0.12–0.02	$y = 0.214x + 6.60$ $r = 0.73$	8.56	529, fig. 3, transformed
		→ *Correlation with S-variant of AGP more evident than with total plasma AGP*					
IV	Carbamazepine	Epilepsy	57–210	0.32–0.17	$y = 0.006x + 3.15$ $r = 0.42$	0.25	121, fig. 1, transformed
V	Carbamazepine-10,11-epoxide	Epilepsy	60–210	0.51–0.33	$y = 0.004x + 1.12$ $r = 0.54$	0.16	121, fig. 1, transformed
VI	Chlorpromazine	Healthy people, renal failure, arthritis, Crohn's disease, cirrhosis	40–258	0.022–0.005	$y = 0.430x + 3.0$ $r = 0.82$	17.2	409, fig. 2, transformed
VII	Disopyramide	Kidney transplant, recipients	35–190	0.68–0.05	$y = 0.079x - 3.64$ $r = 0.85$ (curvilinear!!)	3.16	222, fig. 1
VIII	Disopyramide	Acute myocardial infarction	52–240	0.48–0.08	$y = 0.027x + 0.04$ $r = 0.64$	1.06	131, fig. 5, transformed
IX	Disopyramide	Patients on antiarrhythmic therapy	48–300	0.58–0.15	$y = 0.019x + 0.04$ $r = 0.96$	0.76	78, fig. 3
X	Erythromycin	Cirrhosis	7–95	0.80–0.15	$y = 0.060x + 0.13$ $r = 0.94$	2.39	36, fig. 1, transformed
XI	Imipramine	Healthy people	36–114	0.11–0.06	$y = 0.063x + 7.60$ $r = 0.79$	2.53	408, fig. 2, transformed
XII	Imipramine	Age of healthy people	35–150	0.19–0.09	$y = 0.015x + 5.31$ $r = 0.31$	0.60	6, fig. 3, transformed
XIII	Imipramine	Severe burn injury	34–268	0.19–0.05	$y = 0.044x + 3.63$ $r = 0.78$	1.76	332, fig. 3, transformed
XIV	Imipramine	Healthy people, smoking, habits, sex, age, oral contraceptives use, pregnant women	38–200	0.15–0.08	$y = 0.034x + 4.81$ $r = 0.74$	1.36	287, fig. 2, transformed
XV	Imipramine	Healthy people	47–160(?)	0.10–0.04	$y = 0.076x + 5.48$ $r = 0.76$	3.03	255, fig. 2, transformed
XVI	Imipramine	Cardiac patients	56–346	0.15–0.05	$y = 0.026x + 7.88$ $r = 0.53$	1.04	169, fig. 2
XVII	Imipramine	Isolated AGP (!!)	0–250	0–0.09	$y = 0.041x - 0.19$ $r = 0.96$	1.65	169, fig. 3
XVIII	Imipramine	Rheumatoid arthritis	75–270	0.15–0.07	$y = 0.035x + 4.20$ $r = 0.82$	1.40	288, fig. 1
XIX	Lidocaine	Pregnancy (mother/newborn), oral contraceptives use	4–69	0.74–0.24	$y = 0.026x + 0.57$ $r = 0.62$	1.02	585, fig. 2
XX	Lidocaine	Epilepsy	45–165	0.39–0.17	$y = 0.022x + 0.51$ $r = 0.91$	0.87	441, fig. 2
XXI	Lidocaine	Healthy people	43–137	0.40–0.20	$y = 0.026x + 0.50$ $r = 0.96$	1.03	439, fig. 2
XXII	Lidocaine	Myocardial infarction	58–152	0.38–0.21	$y = 0.023x + 0.03$ $r = 0.89$	0.92	440, fig. 1
XXIII	Lidocaine	Cancer	30–300	0.36–0.09	$y = 0.031x + 0.54$ $r = 0.81$	1.24	250, fig. 1, transformed
XXIV	Lidocaine	Renal disease	16–188	0.50–0.14	$y = 0.027x + 0.34$ $r = 0.93$	1.09	206, fig. 4
XXV	Lidocaine	Trauma	58–300	0.45–0.12	$y = 0.020x + 0.16$ $r = 0.97$	0.81	155, fig. 2

TABLE 8

No.	Drug	Disease	AGP range [mg/100 ml]	F range	B/F	$n_{AGP}K_{AGP} \times 10^{-6}$ [M^{-1}]	Ref.
XXVI	Lidocaine	Trauma, in four patients observed	194–298	0.22–0.12	$y = 0.029x - 1.83$ $r = 0.92$	1.15	155, fig. 4
			112–230	0.31–0.18	$y = 0.017x + 0.27$ $r = 0.79$	0.69	
			136–244	0.31–0.15	$y = 0.027x - 1.17$ $r = 0.96$	1.08	
			120–195	0.31–0.16	$y = 0.040x - 2.88$ $r = 0.99$	1.62	
XXVII	Methadone	Healthy people	28–120	0.13–0.07	$y = 0.054x + 5.21$ $r = 0.68$	2.18	436, fig. 1b, transformed
XXVIII	Methadone	Arthritis, hypoalbuminemia, healthy people	25–160	0.21–0.04	$y = 0.063x + 4.13$ $r = 0.70$	2.52	436, fig. 2, transformed
XXIX	Methadone	Cancer	41–251	0.25–0.06	$y = 0.035x + 1.25$ $r = 0.76$	1.39	7, fig. 1
XXX	Meperedine	Pregnancy (maternal/fetal plasma)	13.3–68.8	0.53–0.31	$y = 0.015x + 0.91$ $r = 0.60$	0.60	367, fig. 1
XXXI	Nortriptyline	Depressive patients	35–148	0.14–0.02	$y = 0.169x - 2.60$ $r = 0.49$	6.78	529, fig. 2, transformed
XXXII	Nortriptyline	Depressive patients	19–118 (concentration of S-variant of AGP)	0.12–0.02	$y = 0.316x - 1.77$ $r = 0.77$	12.6	530, fig. 4, transformed
		→ *Correlation with S-variant of AGP more evident than with total plasma AGP*					
XXXIII	Perazine	Schizophrenic patients	45–124	0.044–0.029	$y = 0.091x + 19.1$ $r = 0.63$	3.65	465, fig. 3, transformed
XXXIV	Perazine	Psychiatric patients	67–163	0.06–0.03	$y = 0.122x + 9.08$ $r = 0.79$	4.87	84, fig. 2, transformed
XXXV	Perazine	Healthy people	53–140	0.06–0.03	$y = 0.086x + 14.8$ $r = 0.38$	3.43	84, fig. 2, transformed
XXXVI	Prazosin	Healthy people	64–284(?)	0.10–0.025	$y = 0.149x + 2.55$ $r = 0.97$	5.74	130, fig. 4B
XXXVII	Prednisolone (neutral drug!)	Isolated AGP (!!)	25–500	0.98–0.58	$y = 0.001x + 0.074$ $r = 0.91$	0.04	353, fig. 7
XXXVIII	Propranolol	Pregnancy (mother/newborn) oral contraceptives used	4–64	0.45–0.12	$y = 0.069x + 2.03$ $r = 0.66$	2.77	585, fig. 3
XXXIX	Propranolol	Elderly patients with acute illness	44–313	0.25–0.02	$y = 0.118x - 0.91$ $r = 0.85$	4.6	397, fig. 1
XL	Propranolol	Acute myocardial infarction	24–184	0.14–0.04	$y = 0.072x + 7.39$ $r = 0.66$	2.89	449, fig. 1
XLI	Propranolol	Healthy people	48–204(?)	0.12–0.05	$y = 0.064x + 5.40$ $r = 0.85$	2.56	450, fig. 4
XLII	Propranolol	Healthy people, renal failure, arthritis, Crohn's disease, cirrhosis	40–268	0.18–0.03	$y = 0.071x + 3.80$ $r = 0.77$	2.85	409, fig. 1, transformed
XLIII	Propranolol	Healthy people, elderly patients with acute illness	45–295	0.22–0.03	$y = 0.095x - 0.02$ $r = 0.88$	3.81	396, fig. 1
XLIV	Propranolol	Healthy people, elderly patients with acute illness	46–272	0.22–0.03	$y = 0.096x + 0.02$ $r = 0.88$	3.85	398, fig. 3
XLV	Propranolol	Smoking effect	43–100	0.20–0.09	$y = 0.081x + 0.92$ $r = 0.73$	3.26	46, fig. 1
XLVI	Propranolol	Obesity	36–133	0.15–0.07	$y = 0.058x + 3.67$ $r = 0.88$	2.32	48, fig. 1
XLVII	Propranolol	Cancer and its treatments	41–256	0.28–0.06	$y = 0.053x + 0.45$ $r = 0.93$	2.1	8, fig. 1
XLVIII	Propranolol	Healthy people	23–132	0.14–0.02	$y = 0.175x + 5.50$ $r = 0.67$	7	16, fig. 3

TABLE 8—Continued

No.	Drug	Disease	AGP range [mg/100 ml]	F range	B/F	$n_{AGP}K_{AGP} \times 10^{-6}$ [M^{-1}]	Ref.
IL	Propranolol	Moderately obese male subjects	45–190	0.15–0.08	$y = 0.030x + 4.43$ $r = 0.73$	1.20	47, fig. 1
L	Propranolol	Arthritis, disseminated lupus, cancer, bacterial infection	90–410	0.11–0.02	$y = 0.135x + 0.63$ $r = 0.88$	5.4	107, fig. 4
LI	Propranolol	Isolated AGP (!!)	20–400	0.50–0.07	$y = 0.028x - 0.05$ $r = 0.97$	1.13	107, fig. 1
LII	Propranolol	Isolated AGP in presence of HSA (4 g/100 ml) (!!)	20–400	0.17–0.02	$y = 0.096x + 3.59$ $r = 1.0$	3.84	107, fig. 1
→ *isolated AGP does not behave like AGP in serum; HSA potentiates binding to AGP; extent of potentation depends on lipids associated with AGP and HSA*							
LIII	Propranolol	Malnutrition	45–200	0.30–0.07	$y = 0.039x + 1.60$ $r = 0.71$	1.56	252, fig. 1, transformed
LIV	Quinidine	Healthy people	48–208(?)	0.33–0.15	$y = 0.017x + 1.71$ $r = 0.86$	0.67	377, fig. 3
LV	Quinidine	Traumatic injury	113–300	0.11–0.05	$y = 0.051x + 2.94$ $r = 0.88$	2.04	154, fig. 3
LVI	Triazolam	Patients on dialysis	72–205	0.15–0.06	$y = 0.051x + 3.21$ $r = 0.82$	2.05	290, fig. 1
LVII	Verapamil	Liver disease	14–58	0.23–0.07	$y = 0.174x + 3.72$ $r = 0.80$	7.09	187, fig. 3b
LVIII	Verapamil	Healthy people	40–130	0.11–0.06	$y = 0.046x + 6.85$ $r = 0.79$	1.85	338, fig. 1
LIX	Verapamil	Isolated AGP (!!)	0–150	0.44–0.06	$y = 0.082x + 0.95$ $r = 0.99$	3.29	338, fig. 2
LX	Zimelidine	Depressed patients	38–105	0.13–0.05	$y = 0.113x + 3.11$ $r = 0.73$	4.5	101, fig. 3, transformed
LXI	Norzimelidine	Depressed patients	39–107	0.32–0.23	$y = 0.012x + 1.75$ $r = 0.69$	0.46	101, fig. 3, transformed

* F, free fraction; B, bound fraction; B/F, binding ratio (under this heading the relation is given between B/F and the AGP concentration, as expressed by equation 6); y, B/F; x, AGP concentration in mg/100 ml; r, correlation coefficient; n_{AGP}, number of binding sites on AGP; K_{AGP}, association constant of drug for AGP; the value of $n_{AGP}K_{AGP}$ is obtained from equation 6 and given in M^{-1}, assuming a molecular weight of 40,000.
† !!, study done with isolated AGP (in vitro) instead of plasma/serum (in vivo); ?, very high value reported for AGP in serum of normals.

It is not possible to discuss all relationships in table 8 in detail. Instead, in table 9 the data relating to propranolol have been given. Propranolol was chosen because many studies have been done on this compound. Only those studies having $r^2 \geq 0.5$ were taken from table 8. The F test of significance indicates a higher than 99% probability for these relationships. If one takes into account that these data originate from different sources and refer to different diseases, the correspondence in the slope of the various linear relationships is remarkable. According to equation 6, this slope represents $n_{AGP}K_{AGP}$, which should be constant as long as the molecular properties of the AGP have not changed. So despite the fact that heterogeneity can be expected due to the diseases (see section II D), it seems that this heterogeneity does not strongly influence the binding constants of propranolol.

The value of the constant term in the linear relationships in this column of table 9 represents the contribution of HSA and LIPO to B/F. This varies in the various cases described. According to equation 6, this is due to variation in the concentration and number of binding sites of HSA and LIPO.

The linear relationships also allow us to calculate the contribution of AGP to the fraction bound. Examples are given in table 9. By substituting a given AGP concentration in the linear relationship (second column), the corresponding B/F, and therefore B value, can easily be calculated. This has been done for three values of the AGP concentration, namely, zero, 73, and 219 mg/100 ml. Note that the average value of the AGP concentration in normal conditions (see section III A) is 73 mg/100 ml. In comparing these B values, one should take the standard errors into account. It is then evident that the calculated values of B as predicted from the various studies are very consistent, as can be seen from the last three columns in table 9.

The linear relationships further permit one to calculate the contribution of AGP to the total binding in the following way. The value of $(B/F)_{AGP}$ can be calculated for a given value of the AGP concentration. Dividing this by the value of the total B/F gives a number which

represents the fraction of the total drug bound that is accounted for by AGP. The last column in table 9 gives some numbers for an AGP concentration of 73 mg/100 ml. The results of the various studies show that AGP accounts for more than 50% of the binding.

In table 10 the binding parameters in plasma for AGP and HSA are summarized. These data were obtained from the fitting of Scatchard plots measured in plasma on the assumption of the presence on AGP and HSA of two classes of binding sites, one with a high affinity and a low capacity and the other one with a low affinity and a high capacity. From these parameters too it is possible to estimate the relative contribution of AGP and HSA to the total plasma binding. This method is a different way of approaching the problem discussed in this section. However, as only a very limited number of studies have been reported, a detailed comparison cannot be made.

Pike et al. (412, 414, 415) and Suzuki et al. (517) used plasma that was deficient in several plasma protein fractions in order to study the binding of acidic, neutral, and basic drugs in plasma. They found that the binding of basic drugs decreased considerably in AGP-deficient plasma. A decrease was observed for acidic and neutral drugs only in HSA-deficient plasma in accordance with the evidence presented above.

It is clear that the data presented in this section confirm that AGP makes an important contribution to the binding of many drugs.

Displacement studies have been performed in order to obtain information about the possibility of clinically relevant competition phenomena in vivo (158, 197, 337, 343, 362–364, 401, 460–465, 544, 581, 588). McElnay and D'Arcy (337) reported recently that the clinical importance of drug displacement during combined drug ther-

TABLE 9

Further analysis of propranolol binding data from table 8

No.*	$y = ax + b$†	F test of significance	r^2	B [AGP] = 0	B [AGP] = 73 mg/100 ml	B [AGP] = 219 mg/100 ml	Fraction of bound drug, bound by AGP at [AGP] = 73 mg/100 ml
XXXIX	$y = 0.118\ (0.007)x - 0.91\ (0.86)$	1,102 = 285	0.74		0.88 (0.01)	0.96 (0.003)	1.12 (0.16)
XLI	$y = 0.064\ (0.009)x + 5.40\ (1.10)$	1,19 = 48	0.72	0.84 (0.03)	0.91 (0.01)	0.95 (0.005)	0.46 (0.09)
XLII	$y = 0.071\ (0.007)x + 3.80\ (0.80)$	1,78 = 111	0.59	0.79 (0.03)	0.90 (0.01)	0.95 (0.004)	0.58 (0.08)
XLIII	$y = 0.095\ (0.007)x - 0.01\ (0.086)$	1,55 = 185	0.77	0.00 (1.06)	0.87 (0.02)	0.95 (0.004)	1.00 (0.16)
XLIV	$y = 0.096\ (0.008)x - 0.02\ (0.81)$	1,40 = 138	0.78	0.00 (1.27)	0.87 (0.02)	0.95 (0.004)	1.00 (0.16)
XLVI	$y = 0.058\ (0.010)x + 3.67\ (0.93)$	1,9 = 31	0.78	0.79 (0.04)	0.89 (0.01)	0.94 (0.008)	0.54 (0.12)
XLVII	$y = 0.053\ (0.004)x + 0.45\ (0.56)$	1,21 = 137	0.87	0.31 (0.27)	0.81 (0.02)	0.92 (0.006)	0.90 (0.15)
L	$y = 0.135\ (0.019)x + 0.63\ (3.39)$	1,14 = 51	0.79	0.39 (1.28)	0.91 (0.03)	0.97 (0.006)	0.94 (0.35)
LI	$y = 0.028\ (0.002)x + 0.05\ (0.41)$	1,12 = 216	0.95	0.05 (0.37)	0.68 (0.05)	0.86 (0.012)	0.98 (0.21)
LII	$y = 0.096\ (0.002)x + 3.59\ (0.42)$	1,11 = 2,224	0.99	0.78 (0.02)	0.91 (0.00)	0.96 (0.001)	0.66 (0.03)
LIII	$y = 0.039\ (0.006)x + 1.60\ (0.68)$	1,38 = 38	0.50	0.61 (0.10)	0.82 (0.03)	0.91 (0.012)	0.64 (0.15)

* The numbers in the first column refer to the compounds in table 8.

† In the second column, y represents B/F and x represents the AGP concentration in mg/100 ml. Numbers in parentheses in this and in other columns in this table represent the standard error in this parameter. The standard error in the value of B, denoted by S_B, follows from the relationship $S_B = (1 + y)^{-2} \cdot S_y$.

TABLE 10

Survey of binding parameters for AGP and HSA in plasma

No.	Category	Drug	$n_{AGP}P_{AGP}$*	K_{AGP} [M^{-1}]†	$n_{HSA}P_{HSA}$	K_{HSA} [M^{-1}]	Ref.
I	Anesthetic	Bupivacaine	*pH 7.4 → 7.0 pH dependent*		*pH 7.4 → 7.0 pH undependent*		140
			$(1.56 \rightarrow 2.14) \times 10^{-5}$	$(1.69 \rightarrow 0.6) \times 10^6$	$0.53 \rightarrow 0.21$	$(4.21 \rightarrow 5.03) \times 10^3$	
II	Tricyclic antidepressant	Amitriptyline	1.6×10^{-4}	5.9×10^4	4.1×10^{-3}	7.3×10^2	83
III	Tricyclic antidepressant	Nortriptyline	3.6×10^{-4}	1.8×10^4	1.8×10^{-3}	1.4×10^3	83
IV	Tranquilizer	Thioridazine		6.39×10^7			381
V	Beta-blocker	Alprenolol		$(3–5) \times 10^5$			236
VI	Beta-blocker	Oxprenolol	8×10^{-6}	1.3×10^6			44
VII	Beta-blocker	Propranolol	Binding in serum deficient in AGP decreases, but no effect in serum deficient in HSA				412 414
VIII	Beta-blocker	Propranolol	Stereoselective binding to AGP of same order as to plasma, but different in HSA				557
IX	Beta-blocker	Propranolol	2.04×10^{-5}	5.87×10^5			44
X	Antiarrhythmic	Quinidine	Binding in serum deficient in AGP decreases considerably				412
		Quinidine	3.49×10^{-5}	1.17×10^5	3.14×10^{-3}	1.33×10^3	154
XI	Antiepileptic	Carbamazepine	2.2	2.4×10^4	9	4.6×10^2	340

* $n_{AGP}P_{AGP}$ and $n_{HSA}P_{HSA}$, binding capacity to AGP and HSA, respectively, in plasma, using Scatchard plots.

† K_{AGP} and K_{HSA}, affinity constant to AGP and HSA, respectively, in plasma, calculated from Scatchard plots.

apy has been overestimated because physiological drug concentrations are generally lower than the concentrations used in in vitro studies. Goolkasian et al. (197), who studied the displacement of lidocaine, concluded from their results that a clinically significant displacement interaction of the drugs studied occurs only when bupivacaine and lidocaine are used in combination. McNamara et al. (343) reported earlier that clinical concentrations of bupivacaine, disopyramide, and quinidine increase the lidocaine concentrations. Mueller et al. (364), who studied the drug displacement between psychotropics, concluded that competition phenomena in vivo may occur for methaqualone and thioridazine. Further binding studies in plasma using several combinations of drug will probably give more information about the clinical relevance of these competition phenomena in vivo.

B. Binding of Basic and Neutral Drugs to Alpha-1-acid Glycoprotein in Vitro

The binding of drugs to AGP in plasma has been discussed in section IV A. A different approach to the study of drug-protein interaction can be followed by first isolating the binding protein from plasma, redissolving the isolated protein in an appropriate solvent (generally an aqueous buffer solution), and using this protein solution for binding experiments. Studies of this type performed with AGP or HSA will be referred to as isolated AGP or isolated HSA binding studies, in order to distinguish them from the binding studies in plasma. Sometimes a mixture of AGP and HSA was used. Results of studies of this type done on isolated AGP or HSA are collected in table 11. In columns 4 and 5 of table 11, the free fractions measured in solutions of isolated AGP or HSA at variable concentrations (F_{AGP} and F_{HSA}, respectively) are reported so that the contribution that each of these proteins makes to the total plasma binding can be estimated. In columns 6 to 9 of table 11, the number of binding sites (n_{AGP} and n_{HSA}) and the binding constants (K_{AGP} and K_{HSA}) of drugs for isolated AGP and HSA are given.

One of the main purposes of this table is to collect data scattered throughout the literature. For a given drug, the combined in vivo and in vitro data can give a picture of the importance of protein binding. Because of the vast amount of data available, it is not possible to discuss the various compounds. Only some general comments will be made.

In a comparison of the binding parameters of the same drug obtained in different studies, it should be noted that the AGP samples were obtained using different methods and that these can have different effects on the physical-chemical properties of AGP, as discussed in section II. It should also be pointed out that, since the AGP concentrations used to determine the free fraction were not the same, different values for the free fraction may result. From studies on binding in solutions of AGP, it follows that often two classes of binding sites are present on AGP. Therefore the in vitro results cannot be compared indiscriminately with the results obtained in plasma reported in section IV A.

Other factors influencing the binding parameters are discussed below in section IV E.

C. Binding of Acidic Drugs to Alpha-1-acid Glycoprotein in Vitro

It is generally assumed that in plasma acidic drugs are mainly bound to HSA. Four recent studies (249, 462, 544, 545) have shown, however, that the association constants of some acidic drugs to AGP are high enough to indicate that binding to AGP will contribute significantly to the total plasma binding of these drugs, especially in diseases in which the concentration of AGP increases and/or of HSA decreases.

The parameters describing the binding of acidic drugs to isolated AGP are summarized in table 12. Israili and El-Attar (249) found that the binding to AGP increased with increasing concentration of AGP and decreasing concentration of the drugs (therapeutic range). The maximum binding of each drug to AGP (at 200 mg/100 ml) was, however, always lower than the binding to HSA (at 4.5 g/100 ml).

Urien et al. (545) studied several acidic drugs with or without a carboxylic group and found that clofibric, fenofibric, salicylic, and valproic acid do not bind to AGP, and that benoxaprofen, indomethacin, and itanoxone at a molar drug/AGP ratio of 0.04 (AGP concentration, 90 mg/100 ml) bind very poorly (table 12). In contrast, the percentages of bound warfarin, acenocoumarol, and phenylbutazone are noticeably higher. The acidic drugs which exhibit a high or intermediate affinity to AGP do not exhibit any carboxyl moiety and share a common specific binding site on HSA, called site I or the warfarin site. By contrast, all the drugs having a poor affinity or no affinity to AGP exhibit carboxyl groups and bind specifically to another HSA binding site, called site II or the diazepam site (527). Moreover, these results demonstrate the existence of only one binding site on AGP, which is the result found earlier for basic drugs. For these acidic drugs, Urien et al. (545) made some calculations to estimate the relative contribution of the drug bound to HSA and AGP in plasma. Acenocoumarol, phenylbutazone, and warfarin would then bind for 90%, 99.3%, and 94%, respectively, to HSA and for 9%, 0.3%, and 5%, respectively, to AGP, whereas the sum of the binding to HSA and AGP is close to the value observed in human plasma.

Comparing the results of Urien et al. (545) and Israili and El-Attar (249), one can conclude that Urien et al. found a much higher affinity of phenylbutazone for AGP than Israili and El-Attar, presumably because Urien et al. used AGP samples from different origins, which led to different binding parameters as will be discussed later in section IV E.

TABLE 11

Survey of binding parameters for the binding of basic and some neutral drugs with isolated AGP and HSA

No.	Drug	Origin of AGP	F_{AGP}	F_{HSA}	n_{AGP}	K_{AGP} [M^{-1}]	n_{HSA}	K_{HSA} [M^{-1}]	Ref.
I	Alfentanil	Miles	AGP concentration dependent, 0.20 → 0.06 (50 → 200 mg/100 ml)	HSA concentration dependent, 0.97 → 0.65 (0.1 → 6 g/100 ml)					348
II	Alprenolol	Behringwerke, 67 mg/100 ml	0.24	0.77					75
		Behringwerke, 66 mg/100 ml	0.45	0.60					42, 43
			$F_{AGP + HSA}$ = 0.29 (same range as in serum)						
III	Amitriptyline	Behringwerke				*Two sites*	6.16	3.7×10^3	83
					0.97 and 1.94	3.4×10^5 and 1.3×10^4			
		Behringwerke	0.165	0.146					82
			$F_{AGP + HSA}$ = 0.10						
			$F_{AGP + HSA + LIPO}$ = 0.064						
		Gift from others	0.334	0.365					413
IV	Aprindine	Behringwerke	Drug concentration dependent, 0.13–0.73	0.15–0.18		*Two sites*			524
					1.1 and 2.9	4.2×10^5 and 8.3×10^3	1	9.8×10^3	
			$F_{AGP + HSA}$ = 0.06 − 0.16 (same range as in serum)		*In solution of mixture of HSA and AGP*				
					0.53	1.4×10^6	0.99	1×10^4	
V	Bupivacaine	Own preparation using modification of method of Hao and Wickerhauser (217)			*pH dependent*		*pH independent*		140
					pH 7.4 → 7.0		*pH 7.4 → 7.0*		
					0.45 → 3.53	(5.3 → 0.146) × 10^5	1.27 → 1.46	(8.98 → 4.87) × 10^2	
		Behringwerke	Concentration dependent, 0.14 → 0.69 (60 → 20 mg/100 ml)						404
		Not mentioned	0.27						410
		AGP (200 mg/100 ml) added to plasma (!!)		Decrease from 0.16 to 0.14 after addition of isolated AGP to plasma					410
VI	Carbamazepine (neutral drug)	Not mentioned	Concentration dependent, 0.71 → 0.90 (150 → 50 mg/100 ml)	0.32	Agree with those calculated in plasma				339

	Sigma	Concentration dependent	Concentration dependent, 0.66 → 0.88 (100 → 50 mg/100 ml)	1.44 → 1.36, 0.65 → 0.52 (4 → 2 g/100 ml)	1.7×10^4	7.5 → 7.33	4×10^2		340
VII	Chlorpromazine	Sigma	Drug concentration dependent, 0.08–0.60	0.20	0.5 and 1	*Two sites* 9.4×10^5 and 5×10^5	≧1	≧6.6×10^3	551
		Miles, defatted				3.4×10^5			282
						3×10^6			158
		Behringwerke	0.076		0.83	3.45×10^6			363
VIII	Ciclazindol	Miles	0.25	0.41					520
IX	Desmethylimipramine	Calbiochem	0.32	0.38	1.3	4.7×10^4	6.8	3.0×10^2	254, 255
X	Diazepam (neutral drug!!)	Behringwerke			1	6.3×10^4			462
		Own preparation and defatted by charcoal				4×10^4 (by drug displacement)			282
		Not mentioned	0.81						5
		Not mentioned	Decreases after addition of AGP to HSA solution from 0.0156 → 0.0109	HSA concentration dependent, 0.013 → 0.024 (5 → 2.3 g/100 ml)					442
XI	Dipyridamole	Behringwerke				*Two sites*			157
					0.9 and 0.9	1.55×10^7 and 4×10^5			
		Own preparation			1	6.25×10^5			514
		Own preparation			1	8×10^5		$n_{HSA}K_{HSA} = 5.7 \times 10^4$	281
XII	Disopyramide	Sigma	Drug concentration dependent, 0.14–0.75		0.2	1.0×10^6			313
		Not mentioned	Drug concentration dependent, 0.35–0.97 AGP concentration dependent, 0.15 → 0.75 (140 → 40 mg/100 ml)	Drug concentration dependent, 0.81–0.98	0.256 and 0.606	*Two sites* 8.84×10^5 and 2.43×10^4			133
		Sigma				Stereoselective $R(-) = 5.12 \times 10^5$ $S(+) = 8.9 \times 10^5$ Racemic = 6.2×10^5			315
		Sigma (600 mg/100 ml!!)			0.02(!!)	9.5×10^5			317

TABLE 11—Continued

No.	Drug	Origin of AGP	F_{AGP}	F_{HSA}	n_{AGP}	K_{AGP} [M^{-1}]	n_{HSA}	K_{HSA} [M^{-1}]	Ref.
		By AGP-contaminated HSA samples		Dependent on HSA samples, 0.95–0.67		Dependent on HSA samples (1.7–3.3) × 10^6		(3 × 10^2) – (2 × 10^5)	
		Addition of human AGP to rabbit serum	Decrease of free fraction after AGP addition						244
		Behringwerke	AGP concentration dependent, 0.19 → 0.57 (200 → 50 mg/100 ml)	1.0					78
XIII	Doxepin	Sigma	AGP concentration dependent, 0.28 → 0.69 (120 → 30 mg/100 ml)	HSA concentration dependent, 0.46 → 0.62 (5 → 3 g/100 ml)					552
XIV	Erythromycin	Behringwerke	0.45	0.91	1	3.5 × 10^4	$n_{HSA}K_{HSA}$ = 1 × 10^2		420
XV	Etidocaine	Commonwealth Serum Laboratory	0.07						357
		Not mentioned	0.17	Addition of AGP to plasma decreases free fraction from 0.128 to 0.064					410
XVI	Fentanil	Miles	AGP concentration dependent, 0.35 → 0.70 (150 → 50 mg/100 ml)	HSA concentration dependent, 0.50 → 0.95 (6 → 0.1 g/100 ml)					348
XVII	Fluphenazine	Own preparation and defatted by charcoal				2.6 × 10^5 (by drug displacement)			282
XVIII	Haloperidol	Behringwerke				*Two sites*			462
					2 and positive cooperativity	7.5 × 10^3 and positive cooperativity			
		Own preparation and defatted by charcoal				6 × 10^4 (by drug displacement)			482
XIX	Imipramine	Behringwerke	0.31	0.54					75
		Calbiochem	0.12	0.46					255
		Calbiochem	0.12	0.46	1.1	9.2 × 10^4	7	2.3 × 10^2	254
	Imipramine	Own preparation and defatted by charcoal			0.5	Defatted 2.8 × 10^5 before defatting 1.5 × 10^5	0.2	1.1 × 10^5	282
					More sites at higher drug levels				
		Behringwerke	0.30		1.1	2.43 × 10^5			363
									364

		Behringwerke				*Two sites*				462
					1 and 2	2.2×10^5 and 4.8×10^4				
XX	Ketamine	Sigma	AGP concentration dependent, 0.79 → 0.90 (100 → 50 mg/100 ml)	HSA concentration dependent, 0.72 → 0.79 (5 → 3 g/100 ml)						135
XXI	Lidocaine	Gift from others	0.77							197
		AGP added to plasma	Addition of AGP (50 mg/100 ml) to serum decreases free fraction from 0.29 to 0.15							
		AGP added to cord serum	Addition of AGP (200 mg/100 ml) to plasma decreases free fraction from 0.36 to 0.14							410
		Plasma deficient in AGP (!!)	Addition of AGP to cord serum decreases free fraction from 0.44 to 0.25 which is in same range as found in serum of adults							411
			Removal of AGP from plasma increases free fraction from 0.3 to 0.8							
XXII	Loxapine	Own preparation				2.4×10^5 (by drug displacement)				282
XXIII	Methadone	Sigma	0.2	0.84		*Two sites*		$n_{HSA}K_{HSA} = 3.2 \times 10^2$		7
					0.38 and 8.4	4×10^5 and 6.2×10^2				
		Own preparation	AGP concentration dependent, 0.09 → 0.92 (200 → 67 mg/100 ml)	0.64						436
			Addition of isolated AGP to plasma or a solution of HSA decreased free fraction with increasing AGP concentration							
XXIV	Metaprolol	Behringwerke	0.98	0.85						42, 43
			$F_{AGP+HSA} = 0.80$, lower than in serum							
XXV	Meperidine	Behringwerke	AGP concentration dependent, 0.80 → 0.96 (60 → 20 mg/100 ml)	0.82						367
		Gift from others	0.68	0.89						242
XXVI	Mianserin	Sigma	Drug concentration dependent, 0.25 → 0.73 (10^{-5} M → 6×10^{-4} M)	Drug concentration dependent, 0.58 → 0.80		*Two sites*		*Two sites*		491
					1.25 and 5.8	1.14×10^5 and 3.37×10^3	0.85 and 3.7	1.28×10^4 and 2.33×10^3		
XXVII	Nicergoline	Own preparation			0.94	1.84×10^4	1.3	6.1×10^3		433
		Desialylated AGP			0.94	2.16×10^4				
		Carboxymethylated AGP			0.94	1.12×10^4				
		Desialylated and carboxymethylated AGP			0.94	0.61×10^4				

TABLE 11—Continued

No.	Drug	Origin of AGP	F_{AGP}	F_{HSA}	n_{AGP}	K_{AGP} [M^{-1}]	n_{HSA}	K_{HSA} [M^{-1}]	Ref.
XXVIII	Nortriptyline	Behringwerke				*Two sites*	5.2	4.4×10^2	83
					0.97 and 0.97	1.2×10^5 and 2×10^4			
		Behringwerke	0.32	0.42					82
			$F_{AGP+HSA} = 0.185$						
XXIX	Oxprenolol	Behringwerke	0.28	0.78					42, 43
			$F_{AGP+HSA} = 0.12$						
			Same as in serum						
		Sigma	0.25	0.80		*Two sites*			44
					0.2 and not mentioned	1.9×10^6 and not mentioned			
XXX	PCR 2362	Behringwerke		0.18	3	3.3×10^4	$n_{HSA}K_{HSA} = 7.1 \times 10^3$		195
XXXI	Perazine	Behringwerke				*Two sites*		*Two sites*	83
					0.97 and 3.9	7.2×10^5 and 7.4×10^3	2 and 8	4.3×10^3 and 4.1×10^2	
		Not mentioned				3.8×10^5 (by drug displacement)			460
		Behringwerke	0.069	0.114					82
			$F_{AGP+HSA} = 0.045$						
			Same as in serum						
		Behringwerke				*Two sites*			462
					1 and 4	3.8×10^5 and 4.2×10^3			
XXXII	Phencyclidine	Gift from others	0.36	0.76					190
		Sigma	AGP concentration dependent, 0.90 → 0.60 (200 → 50 mg/100 ml)	0.81		1.74×10^4			390
			$F_{AGP+HSA} = 0.25 \rightarrow 0.54$		In mixture of AGP and HSA enhanced affinity to AGP, 7.72×10^4				
		Sigma Calbiochem	0.87	0.87					31
XXXIII	Phenothiazin derivatives	Not mentioned				For different derivatives between $(0.4–11) \times 10^4$ (by drug displacement)			460
XXXIV	Perphenazine	Sigma	Drug concentration dependent 0.15 (<10^3 ng/ml) 0.60 (>10^3 ng/ml)	0.27	0.5 and 1.0	*two sites* 3.4×10^5 and 1×10^4	$n_{HSA}K_{HSA} = 4.6 \times 10^3$		551
XXXV	Pindolol	Behringwerke	0.70	0.82					42, 43
			$F_{AGP+HSA} = 0.44$, same as in serum						
		Behringwerke	Drug concentration dependent 0.35 (<5×10^3 ng/ml) 0.90 (>5×10^3 ng/ml)	0.82	1.4	7.1×10^4			305

XXXVI	Pindolol-related compounds	Behringwerke				In the range of (10^4–10^6)		305
XXXVII	Prazosin	Not mentioned	0.35	0.09				200
XXXVIII	Progesterone (neutral drug!!)	Own preparation using chromatography (type c) or ethanolic methods			0.2	9.4×10^5		181
					Type p = type c delipidated			182
					0.9	10.8×10^5		
					Type p recombined with lipid from type c			
					0.17	8.5×10^5		
					Ethanolic precipitation			
					1	8×10^5		
		Gift from others	0.10	0.18				567
		Sigma, native and desialylated	Desialylation, no effect; 0.15		1	3.2×10^5		582
XXXIX	Propranolol	Sigma	Drug concentration dependent 0.17(<10^3mg/ml) 0.4 (>10^3mg/ml)	0.53				551
		Behringwerke	0.31	0.45				41, 42
			$F_{AGP+HSA} = 0.11$, same as in serum					
		Behringwerke	Drug concentration dependent, 0.40–0.95	Drug concentration dependent, 0.45–0.53	$n_{AGP}K_{AGP} = 3.05 \times 10^4$		$n_{HSA}K_{HSA} = 1.8 \times 10^3$	194
		Own preparation and defatted by charcoal				1×10^5 (by drug displacement)		282
	Propranolol	Sigma	Stereoselective $F^-_{AGP} = 0.23^*$ $F^+_{AGP} = 0.30$ $F^{\pm}_{AGP} = 0.26$	0.50				11
		Sigma	0.30	0.60	*Two sites*			44
					0.6 and not mentioned	2.44×10^5 and not mentioned		
		Behringwerke	0.21		1.05	1.13×10^5		363
		Addition of AGP to fetal serum	Increase of binding in fetal serum after addition of AGP to same range as in serum of adults					411
		Sigma, native and desialylated	Drug concentration dependent, 0.05 → 0.17 (0.4 → 2×10^{-6} M)		*Native*			582
					1	8.4×10^5		
					Desialylated			
					1	6×10^5		

TABLE 11—Continued

No.	Drug	Origin of AGP	F_{AGP}	F_{HSA}	n_{AGP}	K_{AGP} [M^{-1}]	n_{HSA}	K_{HSA} [M^{-1}]	Ref.
XL	Quinidine	Not mentioned	0.47	0.61					415
			$F_{AGP+HSA}$ = 0.23, same range as serum						
		AGP added to plasma	Decrease of free fraction in plasma after AGP addition depending on amount added						172
XLI	Thioridazine	Own preparation and defatted by charcoal				8×10^5 (by drug displacement)			282
		Hoechst Swedish			0.93	6.3×10^7		4.9×10^4	381
XLII	Thiothixene	Own preparation and defatted by charcoal				2.4×10^5 (by drug displacement)			282
XLIII	Ticlopidine	Behringwerke		0.12	3	8.9×10^4	$n_{HSA}K_{HSA} = 9.4 \times 10^3$		195
XLIV	Timolol	Behringwerke	0.73	0.93					42, 43
			$F_{AGP+HSA}$ = 0.44, same as in serum						
XLV	Triazolam	AGP added to serum	Increase of drug binding in serum with increasing AGP added						290
XLVI	Trifluoperazine	Sigma	Drug concentration dependent 0.03 (<10^3 ng/ml) 0.20 (>10^3 ng/ml)	0.08	1 and 3	*Two sites* 6×10^5 and 2×10^4	$n_{HSA}K_{HSA} = 3.3 \times 10^4$		551
XLVII	DAPN (fluorescent probe!!)	Sigma				2×10^6 and two weaker sites			4

* F^- and F^+, free fractions of the diastereomeric drug components, respectively.

TABLE 12
Survey of binding parameters reported for the binding of acidic drugs with AGP

No.	Drug	F_{AGP}*	F_{HSA}	n_{AGP}	K_{AGP} [M^{-1}]	Ref.
I	Folic acid	0.97	0.77			249
II	Indomethacin	0.40	0.09	0.3	1.86×10^6	
III	Methotrexate	0.99	0.60			249
IV	Phenylbutazone	0.73	0.07	1.7	5.25×10^3	249
V	Phenytoin	0.67	0.34			249
VI	Probenecid	0.99	0.08			249
VII	Retinoic acid	0.67	0.58			249
VIII	Sulfinpyrazone	0.70	0.17	0.6	2.40×10^3	249
IX	Tolmetin	0.99	0.33			249
X	Acenocoumarol	0.15		1.08	2.01×10^5	545
XI	Benoxaprofen	0.90				545
XII	Indomethacin	0.90				545
XIII	Itanoxone	0.90				545
XIV	Phenylbutazone	0.74		0.71	3.50×10^4	545
XV	Warfarin	0.12		1.09	2.12×10^5	545
XVI	Phenobarbital			*Two sites*		462
				1 and not mentioned	8×10^2 and positive cooperativity	

* F_{AGP}, free fraction in AGP solution (200 mg/100 ml in ref. 249 and 90 mg/100 ml in ref. 545, respectively); F_{HSA}, free fraction in HSA solution (4.5 g/100 ml).

Not included in table 12 are recent results on the binding to AGP of the acidic drug apazone (544).

D. Nature and Number of Binding Sites on Alpha-1-acid Glycoprotein

Several models are used to calculate the number of binding sites and the binding constant (table 13, no. VIII; section IV, A and E). From the literature it follows that in some cases a particular method can result in an incorrect estimate of the binding parameters (1, 40, 417). Therefore, care should be taken when using a particular analyzing procedure. It is advisable to use a computerized method (365).

The differences between the binding-parameters obtained in plasma and obtained in a solution of isolated pure plasma proteins (tables 8, 10–11), as reported by several authors for a defined drug, can be ascribed to the different methods of interpretation and the different origins of the plasma protein fractions used. It should be noted that, in studies dealing with the binding in plasma, authors generally use a model with only one class of binding site(s) for each plasma protein, whereas in studies dealing with the binding in solutions of an isolated plasma protein, they often use a model with two classes of binding sites on one plasma protein.

From the result of the drug displacement studies done with isolated AGP, it can be concluded that on AGP there is only one common binding site for all the basic drugs studied (4, 158, 197, 363, 364, 463) and that the amounts of drug displaced can be correlated with the binding constant. Although this indirect method points to only one single binding site on AGP, other direct methods, such as the curvilinear Scatchard plots, indicate the presence of more than one class of binding sites on AGP (table 11).

The nature of the drug binding to AGP has been the subject of several studies (157, 158, 160, 177, 181, 182, 305, 348, 364, 460–465, 555, 582). The number of reported binding sites on AGP (summarized partly in table 11) can increase to 7, as will be discussed further below. For progesterone and other steroid hormones (181) the number of binding sites on AGP depended on the isolation method used (table 11). Chromatographically purified AGP had a lower binding capacity than alcohol-precipitated AGP or delipidated AGP. Interaction is weakest for the steroids with the highest polarity. The binding of progesterone seems to alter with the conformation of AGP, depending on the neutral salt used (182). Ganguly and Westphal (182) reported on a conformational change of AGP from a more compact globular protein structure towards a random coil, resulting in the reduced availability of the hydrophobic residues near the binding site on AGP. The results of Wallace and Halsall (555) support the hydrophobic nature of the binding of progesterone to AGP. Kerkay and Westphal (272) found that the Δ^4-3-keto group (566) is involved in the interaction of steroids with AGP; they also found that progesterone, cortexone, cortisol, and testosterone associated with AGP at a single primary binding site, whereas estradiol interacted even at 7 and 3 binding sites, respectively, depending on the temperature. Using photoaffinity labeling, Wallace and Halsall (555) found (*a*) that the residues Lys 162 and Glu 136, 140, or 143 were modified and that these modified residues lie at the periphery of a domain whose central region is hydrophobic and (*b*) that the existence of Cys-Cys at 72-165 and the modification of Lys 162 are in agreement with the extreme sensitivity of the progesterone binding to disulfide bridge perturbants. Shami et al. (491) found two classes of binding sites for mianserin on AGP and in total seven binding sites, two of which had a high affinity. Perazine was shown to have one site with a high affinity and about four with a lower affinity (83, 462). Trifluoperazine has four binding sites on AGP, three of which had the same lower affinity (551). Three binding sites with the same affinity are found for ticlopidine and PCR 2362 (195). For dipyridamole at least two binding sites on AGP were found by El-Gamal et al. (157) using Scatchard plot analysis; according to these authors, the high affinity site is located in a hydrophobic part of the protein chain of AGP. For phenothiazine neuroleptics, there is one common binding site on AGP. For these compounds, structural parameters other than the lipophilicity determine the binding (158). Schley (460), studying the binding of phenothiazines, observed that the high affinity of these compounds was caused mainly by the hydrophobic phenothiazine structure itself. The amino acid sequence of the AGP molecule allows one to speculate that the

hydrophobic region of the phenothiazine derivative may interact with the region 21–31 of the amino acid sequence, and that the piperazine side chain may cause ionic interactions with glutamic acids 177 and 178 at the other end of the AGP molecule (461). However, the affinity of the phenothiazines was also influenced by other factors. These results support the conclusion that the interactions of phenothiazines with AGP are not exclusively hydrophobic. Mueller et al. (362–364) also found only one binding site on AGP for a series of psychotropic drugs. Recently Ferry et al. (160) studied the interaction between antidepressants and α_1-adrenergic receptor antagonists as regards their binding to AGP. They found that the binding must be of a hydrophobic nature and that more than one binding site must be involved. Meuldermans et al. (348) reported on the hydrophobic nature of the binding of several analgesics (fentanyl, alfentanil, sulfentanil, and lafentanil) to AGP. Lemaire and Tillement (305) found a correlation between the partition coefficient and the drug binding of beta-blockers by performing drug displacement studies of pindolol. Their results indicate that the AGP binding with beta-blockers must be predominantly of a hydrophobic nature. From studies on displacement of lidocaine by basic drugs, Goolkasian et al. (197) concluded that on AGP there was only one nonspecific site.

Whereas the above-mentioned literature points to the hydrophobic nature of the binding of drugs to AGP, the decrease in the propranolol binding found after desialylation (582) points to an electrostatic interaction as well. Robert et al. (433) also observed a decrease in the nicergoline binding after desialylation, but only when followed by carboxymethylation of the AGP. Friedman et al. (177) reported recently that desialylation of AGP reduced the binding for chlorpromazine, but not for propranolol, progesterone, and dipyridamole. Drayer et al. (149) tried to describe a relation between the lipophilicity of the drugs and the binding to AGP for a series of antiarrhythmics and for a series of beta-blockers, respectively, but they concluded that factors other than lipophilicity are involved in the drug-protein interaction.

Schley and Mueller-Oerlinghausen (463) recently investigated the binding of various tricyclic neuroleptics and antidepressants to AGP. They could not find a correlation between the association constants of the investigated compounds and their antipsychotic potency or their ionization constant.

Busby and Ingham (97) recently suggested the use of fluorescent probes to study the interaction of AGP with other ligands.

Several studies (11, 28–30, 244, 540, 557) have reported that drug binding in plasma is stereoselective, especially in the case of basic drugs, due to stereoselective binding to AGP. This stereoselectivity of AGP is used nowadays in separation techniques for drugs which involve the use of a chiral AGP column (229–234, 402, 458, 459).

The role played by factors other than hydrophobic forces may become evident when one studies the structure of the several basic compounds used in binding studies. Nearly all of them contain a structure consisting of a tertiary nitrogen, linked via a bridge to an aryl system. The bridge is 2 to 4 atoms large and is composed of carbon and nitrogen, mainly of the type C–C, C–C–C, C–C–C–C, C–C–N, and C–C–C–N. It is reasonable to assume that the aryl system contributes to hydrophobic forces, and that the positively charged tertiary nitrogen contributes to ionic forces.

E. Factors Influencing the Characteristics of the Binding of Drugs to Alpha-1-acid Glycoprotein

In this section we shall discuss the influence of several factors, such as the experimental methods and conditions, the physical chemical properties of AGP, and the method used to interpret the drug binding to AGP. These factors are summarized in table 13. Some additional comments will be made.

Recently Yost and DeVane (592) observed a large diurnal variation in the AGP level in plasma of healthy volunteers, namely, a fluctuation of up to 49% within 24 h, which was sex related. This finding should be taken into account in the interpretation of binding data.

The use of Vacutainers for blood collection or the storage of blood samples in plastic containers can result in a decreased drug binding, due to the presence of plasticizers, such as tris(2-butoxyethyl)phosphate (table 13, no. I). These plasticizers were found to selectively displace basic drugs from their binding sites on AGP. This finding was supported by the fact that plasticizers had no effect on the drug binding in plasma deficient in AGP (412–415).

Experimental conditions such as pH, temperature, buffer composition, methods used for drug level determinations, and serum protein concentrations used need to be rigorously controlled because these factors influence the drug binding (table 13, nos. III–V).

The pH of the drug-containing plasma should be checked before and after dialysis (418). Drug binding in plasma increases with increasing pH (table 13, no. III), except in the case of the binding of alfentanil (348) which proved to be pH independent. It should be pointed out that, up until recently, no one has studied the possible effect of pH on the binding of drugs to isolated AGP. It should be noted that such a pH effect has been demonstrated clearly for HSA. Isolated HSA shows a pH-dependent drug binding due to its conformation transition in the physiological pH range (150, 151, 189, 283, 386, 546, 574–576). The pH of serum can also increase during storage (357). Moreover, it is shown that, during storage of plasma, desialylation of AGP and loss of hexose from AGP can occur (522, 523).

The free fraction can be determined using several direct techniques such as equilibrium dialysis, ultrafiltration, high performance liquid chromatography, ultracentrifugation, and gel filtration (113, 130, 189, 210, 246,

TABLE 13

Factors influencing the characteristics of the binding of drugs to AGP

No.	Factor	Effect	Drug	Ref.
I	Use of Vacutainers for blood collection, or storage in plastic containers	Drug displacement from AGP by plasticizers, resulting in increased free fraction of especially basic drugs	Quinidine	126, 143, 153, 154, 170, 176, 354, 387, 415, 492
			Propranolol	44, 126, 415, 572
			Oxprenolol	44, 74
			Alprenolol	74, 407
			Pindolol	305
			Lidocaine	143, 197, 510
			Chlorpromazine	350
			Imipramine	75, 118, 255, 350
			Amitriptyline	118, 350, 415
			Nortriptyline	118
			Thioridazine	381
			Ketamine	135
			Diazepam	5
			Disopyramide	132
II	Presence of heparin	Heparin increases free fraction of basic drugs; this effect can be suppressed by protamine sulfate	Lidocaine	209
			Imipramine	289
			Propranolol	449, 583, 584
III	Experimental conditions during free fraction affect determination in plasma, such as pH, temperature, buffer, storage effect	Increase of binding with increasing pH in plasma	Neuroleptics	81a
			Beta-blockers	228
			Quinidine	87, 210
			Lidocaine	96, 189, 209, 343, 418
			Ketamine	135
			Bupivacaine	140
			Erythromycin	142, 420
			Progesteron	182
			Etidocaine	357
			Verapamil	187, 220, 239
			Fentanyl	336, 348
			Sufentanil	348
			Lofentanil	348
			Imipramine	289
			Disopyramide	397, 495a
			Thioridazine	381
			Phencyclidine	390
		Temperature effect can be different	Propranolol	398
		Decrease of binding with increasing temperature	Progesterone	181
			Imipramine	289
			Propranolol	398
		Increase of binding with increasing temperature	Erythromycin	420
			Fentanyl	142, 239
		No temperature effect	Disopyramide	495a
		Different buffer types and different ionic strength of the buffers can influence the free drug level	Quinidine	87, 207, 238
			Progesterone	182
			Lidocaine	209, 418
			Fentanyl	239
			Imipramine	289
			Erythromycin	420
		Increased binding during storage	Etidocaine	357
IV	Some factors influence when using equilibrium dialysis:	Volume shift, depending on dialysis time, results in overestima-		40, 87, 93, 140, 189, 207, 227, 243, 247, 251,

TABLE 13—Continued

No.	Factor	Effect	Drug	Ref.
	dialysis time; the with drug spiked side; pH change during equilibrium dialysis; adsorption of drug; presence of organic solvents	tion of free fractions; dialysis time is shorter when plasma or plasma protein fraction side is spiked with drug; pH change, adsorption of drug, and the presence of organic solvents during equilibrium dialysis can change drug binding		289, 292, 309, 316, 322, 341, 360, 379, 398, 418, 460, 463, 495, 495a, 501, 539
V	Method used for the determination of AGP concentration	Different degrees of desialylation of AGP result in a different AGP level		12, 58, 489, 490
VI	Different origins of plasma or AGP sample resulting in different degrees of desialylation of AGP, different content of fatty acids, different degree of polymerization of AGP, occurrence of abnormal AGP in plasma due to disease states, or drug therapy	Contamination of albumin delipidation of AGP during isolation increases binding	Disopyramide Progesterone Bupivacaine Lidocaine	223, 317 181, 565 128 285 58, 73, 489
		Desialylation occurring in several diseases affects binding differently		
		Desialylation of AGP decreases drug binding	Propranolol Chlorpromazine Nicergoline	582 177 433
		Desialylation of AGP has no effect on drug binding	Propranolol, dipyridamole, progesterone	177
		Combination of carboxymethylation and desialylation of AGP decreases drug binding	Nicergoline	433
		Degree of polymerization of AGP depends on purification procedure used and changes the drug binding	Progesterone	211, 212, 507, 508
		Increased content of sialic acid due to treatment with phenobarbital increases binding	Desmethylimipramine	84
VII	Microheterogeneity and variants of AGP	The different molecular weights used influence the magnitude of the binding parameters; the effect of microheterogeneity and the occurrence of several AGP variants on drug binding should be controlled	Not studied until now with exception of Tinuely et al. (529)	15, 529; table 4, section IID
VIII	Interpretation of binding data	Models with different classes of binding sites and different graphical methods are used for the fitting of the experimentally determined data, resulting in different binding parameters	Drugs with their binding parameters are already summarized in tables 7–12	2, 4, 22, 40, 93, 166, 275, 276, 327, 337, 365, 417, 422, 437, 438, 457, 505, 581

292, 394, 395, 398, 412, 414, 415, 463, 505, 517, 549). Parsons and Fan (394) recently reported the loss of propranolol during ultrafiltration by binding to the membrane and a larger continuous loss to the O-ring. Evaluation of the various methods by Kurz et al. (292) led these authors to the conclusion that the values achieved by equilibrium dialysis seem to come closest to the real extent of binding. This is the technique that is used most frequently in binding studies. However, several experimental conditions have to be considered (table 13, no. IV). During equilibrium dialysis a dilution of plasma can occur, due to osmotic equilibration; this will result in a relative overestimation of the free fraction. Levy et al. (309) discussed the dilution effect of plasma in cases where the drug binding was also dependent on the drug concentration. The volume shift that occurs increases with dialysis time (207, 243, 289, 539). Lohman et al. (322) reported recently that the relative overestimation of the free fraction, particularly with highly bound drugs, can be up to 60%, and they concluded that many published data may be incorrect. To attenuate this volume shift, several authors have proposed the addition of dextran to the buffer (316) and the use of competitive equilibrium dialysis (379). Dialysis time can be shortened when the drug is added to the plasma-containing side (341, 384). In order to shorten the dialysis time, Hwang and Bayne (247) proposed the use of a dynamic method for the estimation of the extent of plasma protein binding. Tozer et al. (539) proposed an equation which can be used to correct for the volume shift and for the change in the total drug concentration occurring during dialysis experiments in the plasma-containing compartment. When free fractions are calculated from equilibrium dialysis experiments, one should not use the initial total drug concentration as the total drug concentration, but instead one should use the drug concentration in the plasma compartment at equilibrium (40, 501, 539). One should check for adsorption to the dialysis chambers and the dialysis membranes (93, 360) and the effect on the drug binding of the presence of low concentrations of organic solvents (93, 460). Schley (460) reported that 1 to 5% ethanol decreased the perazine binding by about 12%, whereas adsorption was larger in the buffer-containing dialysis chamber.

Several methods can be used to determine the AGP level in plasma (table 13, no V). These include the radial immunodiffusion procedure of Manzini (12, 328, 329), the electroimmunodiffusion method of Laurell (12, 299), laser nephelometry (57, 416), solid-phase enzyme-linked immunosorbent assay (116, 148, 558), radioimmunoassay (RIA) (185), concanavalin A crossed immunoaffinoelectrophoresis (65–69, 373, 374, 563), fast protein liquid chromatography (536), immunoturbidimetric assay (138, 331), and a fluorimetric method using auramine O (516, 517). In most studies only one of the above-mentioned methods is used, and the various methods are hardly ever compared. Sugiyama et al. (516) found the same AGP concentration using auramine O or RIA, as did Haram et al. (218) using laser nephelometry or radial immunodiffusion. Bordas et al. (73, 74) reported, however, that the amounts of AGP estimated by electroimmunodiffusion in plasma were much lower than those actually present as assayed by radial immunodiffusion, the differences being due to different degrees of desialylation of AGP. The difference in the amounts of AGP revealed by the two immunological methods can be used as a basis for estimating the degree of sialylation of AGP; this can vary during several disease states, such as in liver disease and during inflammation (58, 73, 74, 489, 490). Too high or too low estimates of AGP values influence the binding parameters that are calculated.

Although the physical-chemical properties of AGP preparations can vary considerably, as already discussed in section II, the influence of these physical chemical properties on the drug binding is rarely determined in binding studies (table 13, nos. VI and VII). The binding of progesterone to AGP, being the first drug for which the affinity to AGP was described, proved to be dependent on the isolation method used for the AGP (table 11, no. XXXVIII). AGP isolated with an ethanolic precipitation method had a higher affinity for drugs than AGP isolated following a chromatographical procedure. AGP isolated chromatographically and treated with a mixture of alcohol-acetone had the same affinity to progesterone as AGP isolated with an ethanolic precipitation method. From these results it follows that AGP isolated with different methods can have a different degree of delipidation, which results in altered drug binding. Defatting has also an effect on the stability of AGP (213). The stability, denaturation, and degree of polymerization of AGP, as already discussed in section II, are dependent on the degree to which AGP is defatted and desialylated (212). Polymerization results in two types of polymers (507), each of which has a different biological activity (35, 388, 507) and a different binding to progesterone (508). Desialylation occurring during several isolation procedures for AGP (section II A), especially at low pH, also has an effect on the drug binding (table 11) and can be different for each drug. Wong and Hsia (582) found, for example, that desialylation reduced the propranolol binding, whereas the progesterone binding did not change. Robert et al. (433) found that desialylation had no effect on the nicergoline binding, whereas a combination of desialylation and carboxymethylation decreased the nicergoline binding. Carboxymethylation alone did not influence the nicergoline binding.

V. Concluding Remarks

The literature on AGP has been reviewed up to 1987. From the literature, especially from the studies after 1980, the following conclusions can be drawn:

- physical-chemical properties of AGP, such as the structure and the degree of desialylation of the carbo-

hydrate moiety, the degree of polymerization, the molecular weight, the microheterogeneity, and the binding parameters, can change due to disease states and due to the procedures used for its isolation; more attention should therefore be paid to the methodology of AGP preparation (section II);

- AGP is indeed an acute phase protein, the plasma level of which can be used as a diagnostic and prognostic aid during clinical therapy; this has implications for the monitoring of the free fractions of basic drugs during clinical therapy (section III);
- the large variations observed in the binding ratios of basic drugs in plasma during several physiological and pathological states are correlated with the large variations in the plasma level of AGP; this leads one to the conclusion that AGP plays an important role in the plasma binding of basic drugs (sections III and IV); and
- the experimentally determined characteristics of the binding of basic drugs to AGP are strongly dependent on experimental factors and on the physical-chemical properties of the AGP sample itself; therefore, more attention should be paid to the standardization of the experimental conditions and to the characterization of AGP (sections II to IV).

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