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	Meperidine	60, 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, 181, 133, 136, 186, 222, 223, 230, 244, 264, 313–317, 348, 397, 412, 414
XV	Antiarrhythmic	Quinidine	67, 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, 330, 340, 432, 531
XXIV	Antiepileptic	Phenytoin	45, 411, 462, 549
XXV	Antiinflammatory agent	Naproxen	408
XXVI	Beta-blocker	Alprenolol	42, 43, 75, 136, 235, 238, 408
XXVII	Beta-blocker	Metoprolol	42, 43
XXVIII	Beta-blocker	Oxprenolol	42–45, 271
XXIX	Beta-blocker	Pindolol and 8 related compounds	42, 48, 305
XXX	Beta-blocker	Propranolol	8, 11, 16, 41–46, 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, 462
XXXVII	Psychotropic	Chlorpromazine	158, 176, 282, 359, 363, 409, 462, 549, 551
XXXVIII	Psychotropic	Cyclazindol	520
XXXIX	Psychotropic	Desmethylimipramine	84, 254, 255, 551
XL	Psychotropic	Diazepam	5, 84, 134, 206, 282, 382, 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	158
		Acepromazine	
		Protipendyl	
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	4
		1,8-Anilinonaphtalene sulfonate	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:

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

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 8×10^6 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	$n_{AGP}K_{AGP}$ × 10^{-5} [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	$y = 0.078x + 0.59$ $r = 0.72$	2.95	296, 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	$y = 0.008x + 3.15$ $r = 0.42$	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	$y = 0.480x + 3.0$ $r = 0.83$	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	256, 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	$y = 0.026x + 0.57$ $r = 0.63$	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	$y = 0.023x + 0.08$ $r = 0.89$	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