Molecular Immunology, Vol. 28, No. 4/5, pp. 489–498, 1991
Printed in Great Britain.

0161-5890/91 $3.00 + 0.00
Pergamon Press plc

A POSSIBLE PROCEDURE FOR REDUCING THE IMMUNOGENICITY OF ANTIBODY VARIABLE DOMAINS WHILE PRESERVING THEIR LIGAND-BINDING PROPERTIES

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(*First received* 24 *May* 1990; *accepted in revised form* 17 *September* 1990)

Abstract—It is proposed to reduce the immunogenicity of allogeneic antibody variable domains, while preserving ligand-binding properties, by reducing their antigenicity through replacement of the exposed residues in the framework regions which differ from those usually found in host antibodies. The results of a comparison of representative murine antibody sequences with those of human origin suggest that the number of residues that need to be replaced to "humanize" those antibodies could be small.

INTRODUCTION

Antibodies of predetermined specificity have many potential uses in therapy and diagnosis and hybridoma technology (Koehler and Milstein, 1975) has made possible the generation of virtually limitless amounts of such antibodies. Unfortunately, hybridoma proteins are more easily obtained from rodent sources and the use of those antibodies in human subjects will be hindered by the patients' immune system. Various attempts have been made to make such allogeneic antibodies less immunogenic while preserving their antigen-binding properties.

The immunogenicity of rodent-derived antibodies had been reduced by generating chimeric antibodies in which the variable domains of the rodent proteins were grafted onto constant regions of human molecules (reviewed by Morrison and Oi, 1988). Such chimeric molecules would be expected to possess all the antigen-binding characteristics of the original antibodies, but would retain the immunogenicity of the rodent variable domains.

Further reduction in the immunogenicity of chimeric antibodies had been achieved by Winter and coworkers (Jones *et al.*, 1986; Verhoeyen *et al.*, 1988; Riechmann *et al.*, 1988) by grafting the complementarity-determining regions, or CDRs, of the allogeneic proteins onto human framework regions. In two published applications of this method (Riechmann *et al.*, 1988; Queen *et al.*, 1989), some of the framework residues of the allogeneic antibody, which were thought would ensure a proper structure for the variable domains and a proper interdomain contact, were kept in the "humanized" molecule in an attempt to preserve ligand-binding properties. The "humanized" molecules did exhibit the same ligand-binding specificity as the original antibodies, but with only about one-third of the affinity.

X-ray crystallographic studies have repeatedly demonstrated that the framework structures of the Fvs of different antibodies assume a "canonical" structure regardless of species of origin, amino acid sequence, or ligand-binding specificity. This is generally taken as evidence that the ligand-binding characteristics of an antibody combining site are determined primarily by the structure and relative disposition of the CDRs, although some neighboring framework residues also have been found to be involved in antigen binding (Amit *et al.*, 1986; Colman *et al.*, 1987; Sheriff *et al.*, 1987; Padlan *et al.*, 1989). Thus, if the fine specificity of an antibody is to be preserved, its CDR structures (and probably also some of the neighboring residues), their interaction with each other, and their interaction with the rest of the variable domains must be strictly maintained. This may require the retention of most, if not all, of the many interior and interdomain contact residues; the structural effects of replacing only a few of them cannot be predicted.

It may be possible to simultaneously reduce immunogenicity and strictly preserve ligand-binding properties. Since the antigenicity of a protein is dependent on the nature of its surface (Benjamin *et al.*, 1984), replacing the exposed residues of an allogeneic antibody with those usually found in host antibodies would decrease the probability of its recognition and internalization by antigen-processing cells, specifically by antigen-specific B-cells which play a critical role in priming T-cells (Ron *et al.*, 1983; Kurt-Jones *et al.*, 1988; see also the review by Vitetta *et al.*, 1989). Such

Abbreviations: CDR, complementarity-determining region; Fab, the antigen-binding fragment of an antibody; Fv, the module containing VH and VL, the variable domains of the heavy and light chains, respectively.

a procedure, in the end, then serves to reduce immunogenicity. The judicious replacement of exterior residues should have little, or no, effect on the interior of the domains, or on the interdomain contacts. If the envisioned replacements are confined to the framework regions, especially to only the exposed residues, then the ligand-binding properties of the antibody could be expected to remain unaltered.

This possibility is explored in this paper using as an example the "humanization" of mouse variable domains. First, the available sequence data for the various human variable domain subgroups are analysed in terms of the residues which usually occur at each framework position. Then the differences between human and representative mouse sequences are assessed and correlated with solvent accessibility as deduced from the known three-dimensional structure of human and mouse Fabs. It is found that the number of exposed residues, which need to be replaced to "humanize" mouse variable domains, could be small.

MATERIALS AND METHODS

(a) *Structural data*

The structures that were chosen for the analysis were those of the variable domains of the antibodies KOL and J539. The Fabs of KOL and J539 are those which have been elucidated to the highest resolution and have been subjected to the most extensive refinements so far. The crystal structure of the human KOL Fab had been determined at 1.9 Angstrom resolution (Marquart *et al.*, 1980) and had been refined to an R-value of 1.89; the structure of the mouse J539 Fab had been elucidated at 1.95 Angstrom resolution and had been refined to an R-value of 1.95 (T. N. Bhat, E. A. Padlan and D. R. Davies, in preparation). The atomic coordinates for the KOL and J539 structures are available from the Protein Data Bank (Bernstein *et al.*, 1977) (File 2FB4 for KOL, File 2FBJ for J539).

The solvent accessibility of the individual residues in the KOL and J539 VL and VH was assessed using program MS of Connolly (1983) and programs developed by Sheriff (Sheriff *et al.*, 1985). A radius of 1.7 Angstroms was assumed for the solvent probe; standard van der Waals' radii (Case and Karplus, 1979) were used. The fractional accessibility values for the sidechains (Sheriff *et al.*, 1985; Shrake and Rupley, 1973) were computed as described previously (Padlan, 1990). Exposures were computed in the context of isolated Fvs.

Residues in the interface between VL and VH in the KOL and J539 Fabs were designated as being in contact if they have atoms that come within half an Angstrom of the sum of their van der Waals' radii.

(b) *Sequence data*

A survey was made of the residues occurring at each position in the framework regions of human light and heavy chain variable domains. The sequences were obtained from the compilation of Kabat *et al.* (1987). Only those sequences that are completely determined in the framework regions, 1–23, 35–49, and 57–88 in the light chains, and in the framework regions, 1–30, 36–49, and 66–94, in the heavy chains (numbering of Kabat *et al.*, 1987), were included in the survey. For the fourth framework region, 98–107 in the light chain and 103–113 in the heavy chain, only the residues that could be derived from the known J-minigene segments (Kabat *et al.*, 1987) were considered. Here, the numbering scheme of Kabat *et al.* (1987) is used throughout and pyrollidone carboxylic acids are counted as glutamines.

The human kappa-chain sequences included in the survey were: ROY, AU, REI, HAU, HK101′CL, SCW, WEA, HK137′CL, HK134′CL, DAUDI′CL, WALKER′CL, GAL(1), LAY, WES, Vb′CL, HK102′CL, EU, DEN, AMYLOID BAN, MEV, Vd′CL, Va′CL, KUE, Ve′CL, V13′CL, V18A′CL, V19A′CL, V19B′CL, and V18C′CL in V-kappa subgroup I; NIM, CUM, GM603′CL, FR, and RP M1-6410′CL in V-kappa subgroup II; TI, WOL, SIE, NG9′CL, NEU, GOT, PAY, SON, GAR′, PIE, FLO, GLO, CUR, IARC/BL41′CL, POM, REE, and K-EV15′CL in V-kappa subgroup III; and VJI′CL, VKAPPAIV GERMLINE′CL, PB17IV′CL, and LEN in V-kappa subgroup IV.

The human lambda-chain sequences included in the survey were: NEWM, HA, NIG-64, NEW, BL2′CL, WAH, NIG-77, VOR, RHE, LOC, OKA, COX, and NIG-51 in V-lambda subgroup I; NIG-84, MES, WH, NEI, WEIR, TOG, TRO, BOH, NIG-58, VIL, WIN, and 4A′CL in V-lambda subgroup II; HIL, LAP, GAR, and MOT in V-lambda subgroup III; SH in V-lambda subgroup IV (included for completeness although missing the residue at position 1); BO and MCG in V-lambda subgroup V; AMYLOID-AR, SUT, THO, LBV′CL, and NIG-48 in V-lambda subgroup VI.

The human heavy-chain sequences included in the survey were: EU, SIE, HG3′CL, WOL, ND′CL, and MOT in VH subgroup I; COR, DAW, OU, MCE′, CE-1′CL, HE, SUP-T1 VH-JA′CL, WAH, and HIG1′CL in VH subgroup II; TUR, LAMBDA-VH26′CL, POM, WAS, H11′CL, TEI, BRO′IGM, LAY, GRA′, ZAP, JON, DOB, NIE, 333′CL, 1H1′CL, 1B11′CL, 126′CL, 112′CL, 115′CL, TRO, and KOL in VH subgroup III.

(c) *Comparison of representative mouse and human sequences*

The degree to which mouse variable domains would have to be mutated in order to "humanize" them, was determined by comparing the framework regions of representative sequences from the various mouse subgroups with the known human sequences (Kabat *et al.*, 1987). The human sequence that should serve best for comparison purposes is that which is the most similar to the particular mouse sequence under consideration. However, in view of the possibility

that individual sequences may have errors, the most frequently occurring residue at each position in the various human variable domain subgroups was also used in the comparisons. In many instances, more than one residue is found at high frequency at a given position; in those cases, any amino acid that occurs at least one-fourth as frequently as the most commonly occurring residue was considered a possible alternative in the comparisons. The human subgroup to which each mouse sequence most closely corresponds was determined in this manner; the human sequence to which the mouse sequence is most similar was also determined.

The sequences that were chosen as representative of the various mouse variable domain subgroups were: S107 (Subgroup I), TEPC(CAL20)105 (Subgroup II), TEPC111 (Subgroup III), S107B′CL (Subgroup IV), R16.7 CRI+ (Subgroup V), and TEPC191 (Subgroup VI) of the kappa chains; MOPC104E of the lambda chains; and 36-60 CRI- (Subgroup I(A)), MC101′CL (Subgroup I(B)), MOPC104E (Subgroup II(A)), B1-8′CL (Subgroup II(B)), G5 BB 2.2(AB1) Subgroup II(C)), TEPC15 (Subgroup III(A)), XRPC44 (Subgroup III(B)), HPC76′CL (Subgroup III(C)), and 93G7 CRI+′CL (Subgroup V(A)) of the heavy chains (Kabat *et al.*, 1987). These sequences are the first listed of the sequences in each subgroup in Kabat *et al.* (1987) that are completely determined in all four framework regions. None of the sequences in the VH subgroups V(A) and V(B) in the compilation of Kabat *et al.* (1987) satisfies this criterion. In addition, MOPC21′CL was chosen to represent the miscellaneous mouse heavy chains which have not been assigned to any particular subgroup.

RESULTS

The solvent accessibility of the framework residues in the variable domains of KOL and J539 and the amino acids most frequently occurring at each position in the various subgroups are given in Table 1 for heavy chains, in Table 2 for lambda chains, and in Table 3 for kappa light chains. The residues that contact the opposite domain in the VL–VH interface are indicated in these tables. The results of the comparison of the mouse and human sequences are presented in Table 4.

DISCUSSION

A close examination of the fractional accessibility values presented in Table 1 reveals a very close similarity in the exposure patterns of the VH domains of KOL and J539. Only at positions 88 and 104 are the two patterns drastically different and at these positions one or both proteins have glycine. According to the convention used here (see footnote to Table 1), glycine is designated as being completely exposed if its alpha-carbon is accessible to the solvent probe, otherwise it is designated as being completely buried; thus, the slightest difference in structure could result in different exposure designations for homologous glycine residues. The exposure patterns of their VL domains (Tables 2 and 3) likewise are very similar with large differences only at positions 2, 13, 66, 99, and 101. The conformation of the amino-terminal segments of the KOL and J539 light chains are slightly different, resulting in the difference observed at position 2; at the other positions, one or both proteins again have glycine.

The very close similarity of the exposure patterns for the variable domains of KOL and J539 points to the close correspondence of the tertiary structures and of the dispositions of individual residues in these homologous domains. This is particularly remarkable because (a) these antibodies are from different species, (b) their light chains are of different types (J539 has a kappa light chain, while KOL has a lambda light chain), (c) half of their CDRs, specifically the first and third CDRs in VL and the third in VH, have very different lengths and backbone conformations, and (d) KOL and J539 have only 44 identical residues out of the 79 corresponding positions in the VL framework and 60 out of 87 in VH. An even closer similarity in overall structure and in the exposure patterns might be expected for two molecules that are more similar in sequence than this pair.

By and large, the determination of which human variable domain subgroup an allogeneic domain most closely corresponds to is straightforward. However, in some of the human subgroups presented in Tables 1 to 3, many positions exhibit several possible alternatives. Of the 76 positions in the first three framework regions in VH, 18 in Subgroup I presented more than one possible alternative for the amino acid comparisons, 30 in Subgroup II, and 21 in Subgroup III. Of the 70 positions in the first three framework regions in the kappa light-chain variable domains, three in Subgroup I presented more than one possible alternative, two in Subgroup II, none in Subgroup III, and one in Subgroup IV; of the corresponding 69 positions in the lambda chains, 11 in Subgroup I presented more than one possible alternative, eight in Subgroup II, 28 in Subgroup III, none in Subgroup IV since there is only one available sequence, eight in Subgroup V, and five in Subgroup VI. The existence of several possible alternatives in some of these subgroups, especially in the heavy chains, emphasizes the need for further subdivision; finer subgrouping would allow greater precision in the sequence correlations and greater ease in the identification of the residues which differ between human and non-human antibodies.

A procedure is proposed here for reducing the antigenicity of an allogeneic variable domain while preserving its ligand-binding properties. It is based on the replacement of the residues which differ from those of the host with the corresponding residues in the most similar host sequence. Only those residues which are at least partly exposed in the corresponding domains of KOL or J539 (those with pB, mE, or Ex

Table 1. Solvent exposure of sidechains of framework residues in KOL and J539 Fvs and the residues which occur most frequently at these positions in the various human VH subgroups

	Fractional accessibility						
	KOL		J539		Residues in subgroup		
Position	Residue	Exposure	Residue	Exposure	I	II	III
1	E	1.00 Ex	E	1.00 Ex	Q	Q	E
2	V	0.23 mB	V	0.37 mB	V	V	V M
3	Q	0.82 Ex	K	0.82 Ex	Q	T Q	Q
4	L	0.00 Bu	L	0.10 Bu	L	L	L
5	V	0.87 Ex	L	1.00 Ex	V	R Q K T	V L
6	Q	0.00 Bu	E	0.09 Bu	Q	E	E
7	S	0.94 Ex	S	0.94 Ex	S	S	S
8	G	1.00 Ex	G	1.00 Ex	G	G	G
9	G	0.00 Bu	G	0.00 Bu	A	P	G
10	G	1.00 Ex	G	1.00 Ex	E	A G T	G A
11	V	0.90 Ex	L	0.81 Ex	V	L	L F
12	V	0.25 mB	V	0.25 mB	K	V	V
13	Q	0.71 mE	Q	0.87 Ex	K	K	Q
14	P	0.59 pB	P	0.64 mE	P	P	P
15	G	1.00 Ex	G	1.00 Ex	G	T S	G
16	R	0.73 mE	G	1.00 Ex	S A	E Q	G
17	S	0.66 mE	S	0.75 mE	S	T	S
18	L	0.28 mB	L	0.26 mB	V	L	L
19	R	0.66 mE	K	0.75 mE	R K	T S	R K
20	L	0.00 Bu	L	0.00 Bu	V	L	L
21	S	0.71 mE	S	0.82 Ex	S	T	S
22	C	0.00 Bu	C	0.00 Bu	C	C	C
23	S	1.00 Ex	A	1.00 Ex	K	T	A
24	S	0.00 Bu	A	0.00 Bu	A T V	F V	A
25	S	0.87 Ex	S	1.00 Ex	S	S	S
26	G	1.00 Ex	G	1.00 Ex	G	G	G
27	F	0.10 Bu	F	0.10 Bu	G Y D	F L G	F
28	I	0.85 Ex	D	0.72 mE	T	S	T N
29	F	0.00 Bu	F	0.00 Bu	F	L I	F
30	S	0.74 mE	S	0.83 Ex	S N V I	S	S
36	W	0.00 Bu	W	0.00 Bu	W	W	W
37	V	0.00 Bu	V	0.00 Bu	V	I	V
38	R	0.10 Bu	R	0.31 mB	R	R	R
39	Q	0.15 Bu	Q	0.28 mB	Q	Q	Q
40	A	0.95 Ex	A	0.75 mE	A	P	A
41	P	0.90 Ex	P	0.73 mE	P	P	P S
42	G	1.00 Ex	G	1.00 Ex	G	G	G
43	K	0.86 Ex	K	0.86 Ex	Q R K H	K R	K
44	G	1.00 Ex	G	1.00 Ex	G	A G	G S
45	L	0.00 Bu	L	0.00 Bu	L	L	L
46	E	0.75 mE	E	0.73 mE	E	E	E
47	W	0.10 Bu	W	0.04 Bu	W	W	W
48	V	0.00 Bu	I	0.00 Bu	M V	L I	V
49	A	0.00 Bu	G	0.00 Bu	G	A G	G S A
66	R	0.36 mB	K	0.51 pB	R	R	R
67	F	0.00 Bu	F	0.00 Bu	V	L V	F
68	T	0.87 Ex	I	0.88 Ex	T	T	T
69	I	0.00 Bu	I	0.00 Bu	V M I	I V	I
70	S	0.78 mE	S	0.79 mE	T S	S T	S
71	R	0.11 Bu	R	0.00 Bu	R L A	K V	R
72	N	0.61 mE	D	0.55 pB	D K	D	D N
73	D	0.44 pB	N	0.43 pB	P E T A S	T	D N
74	S	0.85 Ex	A	0.97 Ex	S	S	S
75	K	0.88 Ex	K	0.77 mE	T F	K R	K
76	N	0.69 mE	N	0.68 mE	N S T	N	N
77	T	0.41 pB	S	0.33 mB	T Q	Q	T
78	L	0.00 Bu	L	0.00 Bu	A V	V F	L A
79	F	0.45 pB	Y	0.35 mB	Y	V S	Y F
80	L	0.00 Bu	L	0.00 Bu	M	L	L
81	Q	0.53 pB	Q	0.69 mE	E	T K S I N	Q
82	M	0.00 Bu	M	0.00 Bu	L	M L	M
82a	D	0.73 mE	S	0.58 pB	S V R T	T S N I R	N D
82b	S	0.98 Ex	K	0.96 Ex	S	N S	S
82c	L	0.00 Bu	V	0.00 Bu	L	V M	L
83	R	0.73 mE	R	0.83 Ex	R F I	D T	R E
84	P	0.75 Me	S	0.90 Ex	S	P A	P A
85	E	0.82 Ex	E	0.90 Ex	E	V A	E D
86	D	0.00 Bu	D	0.11 Bu	D	D	D
87	T	0.54 pB	T	0.47 pB	T	T	T
88	G	1.00 Ex	A	0.00 Bu	A	A	A
89	V	0.58 pB	L	0.63 mE	V	T V	V L
90	Y	0.00 Bu	Y	0.00 Bu	Y	Y	Y
91	F	0.00 Bu	Y	0.08 Bu	Y	Y	Y
92	C	0.00 Bu	C	0.00 Bu	C	C	C
93	A	0.00 Bu	A	0.00 Bu	A	A	A T
94	R	0.17 Bu	R	0.15 Bu	R	R H	R P

Table 1—*continued*

Position	Fractional accessibility KOL Residue	KOL Exposure	J539 Residue	J539 Exposure	Residues in subgroup I JH1	I JH2	II JH3	II JH4	III JH5	III JH6
103	**W**	0.09 Bu	**W**	0.07 Bu	W	W	W	W	W	W
104	**G**	0.00 Bu	**G**	1.00 Ex	G	G	G	G	G	G
105	Q	0.93 Ex	**Q**	0.99 Ex	Q	R	Q	Q	Q	Q
106	G	0.00 Bu	G	0.00 Bu	G	G	G	G	G	G
107	T	0.22 mB	T	0.26 mB	T	T	T	T	T	T
108	P	0.99 Ex	L	0.67 mE	L	L	M	L	L	T
109	V	0.00 Bu	V	0.00 Bu	V	V	V	V	V	V
110	T	0.76 mE	T	0.69 mE	T	T	T	T	T	T
111	V	0.00 Bu	V	0.00 Bu	V	V	V	V	V	V
112	S	0.98 Ex	S	0.74 mE	S	S	S	S	S	S
113	S	0.94 Ex	A	0.84 Ex	S	S	S	S	S	S

The one-letter amino acid code is used here. The fractional solvent accessibility values for the individual residues were computed as described by Padlan (1990); residues whose sidechains have fractional accessibility values between 0.00 and 0.20 are designated as being completely buried (Bu), between 0.20 and 0.40 as mostly buried (mB), between 0.40 and 0.60 as partly buried/partly exposed (pB), between 0.60 and 0.80 as mostly exposed (mE), and at least 0.80 as completely exposed (Ex). In the special case of glycine, the residue is considered completely exposed if its alpha-carbon atom is accessible to solvent, otherwise it is considered completely buried. Residues that are involved in the VL–VH contact are shown in bold letters.

Table 2. Solvent exposure of sidechains of framework residues in KOL VL and the residues which occur most frequently at these positions in the various human V-lambda subgroups

Position	Residue	Exposure	Residues in subgroup I	II	III	IV	V	VI
1	Q	1.00 Ex	Q	Q	SF	—	Q	ND
2	S	1.00 Ex	S	S	Y	S	S	F
3	V	0.77 mE	V	A	E	E	A	M
4	L	0.00 Bu	L	L	L	L	L	L
5	T	0.92 Ex	T	T	TK	T	T	T
6	Q	0.00 Bu	Q	Q	Q	Q	Q	Q
7	P	0.62 mE	P	P	P	D	P	P
8	P	1.00 Ex	P	ARP	P	P	P	H
9	S	1.00 Ex	S	S	S	A	S	S
10	—	— —	—	—	—	—	—	—
11	A	0.34 mB	AV	V	V	V	A	V
12	S	0.71 mE	S	S	S	S	S	S
13	G	1.00 Ex	GA	G	VL	V	G	E
14	T	0.73 mE	TA	S	SA	A	S	S
15	P	0.75 mE	P	P	PA	L	PL	P
16	G	1.00 Ex	G	G	G	G	G	G
17	Q	0.69 mE	Q	Q	Q	Q	Q	K
18	R	0.79 mE	R	S	T	T	S	T
19	V	0.21 mB	V	IV	A	V	V	V
20	T	0.62 mE	T	T	RM	R	T	T
21	I	0.00 Bu	I	I	I	I	I	IFM
22	S	0.92 Ex	S	S	T	T	S	S
23	C	0.00 Bu	C	C	C	C	C	C
35	W	0.00 Bu	W	W	W	W	W	W
36	Y	0.00 Bu	Y	YF	Y	Y	Y	Y
37	Q	0.46 pB	Q	Q	Q	Q	Q	Q
38		0.00 Bu	QH	Q	QE	Q	Q	Q
39	L	0.75 mE	LV	H	KR	K	H	R
40	P	0.91 Ex	P	P	PS	P	PA	P
41	G	1.00 Ex	G	G	G	G	G	G
42	M	0.74 mE	T	K	QR	Q	RK	SRG
43	A	0.62 mE	A	A	A	A	A	A
44	P	0.00 Bu	P	P	P	P	P	P
45	K	0.95 Ex	K	K	V	L	K	T
46	L	0.23 mB	L	L	MLP	L	LV	T
47	L	0.15 Bu	L	MIL	V	V	VI	V
48	I	0.00 Bu	I	I	IV	I	I	I
49	Y	0.39 mB	Y	YF	Y	Y	FY	Y
57	G	1.00 Ex	G	G	GE	G	G	G
58	V	0.14 Bu	VI	VI	IV	I	V	V
59	P	0.70 mE	P	SP	P	P	P	P
60	D	0.95 Ex	D	DNL	EQA	D	D	D
61	R	0.31 mB	R	R	R	R	R	R
62	F	0.12 Bu	F	F	F	F	F	F
63	S	0.85 Ex	S	S	S	S	S	S
64	G	0.00 Bu	GA	G	GS	G	G	G
65	S	1.00 Ex	S	S	SY	S	S	S
66	K	0.41 pB	K	K	TSN	S	K	IF*
67	S	1.00 Ex	S	S	S	S	S	S
68	G	1.00 Ex	G	G	G	G	DG	S
69	A	0.71 mE	T	N	TN	H	N	N

(*continued overleaf*)

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