illustrated in Fig. 3. In Fig. 3A is a contour plot of the predicted response of an idealized neuron for visual stimuli occurring at different locations in head-centered coordinate space and viewed at different angles of gaze. For simplicity only one dimension, the vertical meridian, is considered. This contour plot was generated by multiplying a planar gain field, which is a sloping line in one dimension, by a receptive field approximated by a Gaussian and whose center lies on the vertical meridian. The resulting plot predicts that, within the range of eye positions considered, the cell will respond best when the stimulus occurs approximately 20° down in head-centered space when the animal is also looking 20° down. The response profile is also elongated along a diagonal that corresponds to the head-centered coordinate location of the center of the retinal receptive field at the different angles of gaze. A cell with no angle-of-gaze effect would have a gain of one at all eye positions; as a result it would have the same maximum response at every point along this diagonal and would not exhibit tuning for head-centered coordinate locations. Figure 3B shows a contour plot of neural data for an actual neuron with gain and receptive field properties similar to those of the cell modeled in Fig. 3A. The similarity of the two plots, both in this case and for seven other neurons for which there were sufficient data to enable this type of analysis, indicates that a simple multiplication of the retinal receptive field by the gain field is sufficient to approximate the spatial tuning behavior of these neurons.

These area 7a cells do not encode the spatial location of stimuli independent of eye position; however, computer simulations we have made show that such an eye position–independent response can be achieved by combining the activity of several neurons that have the same maximum head-centered location responses, but for different optimum angles of gaze. Such a convergence may take place in the projection of area 7a onto another brain structure. However, since this information already exists in the response of subpopulations of neurons in area 7a, it is likely that spatial locations are encoded in the activity of groups of these neurons and may not require an additional step of convergence.

Finally, there is the question of how space is represented topographically across area 7a. At present we do not have sufficient data to address this issue; one attractive possibility is that the space-tuned peaks of activity are ordered to form a systematic map of head-centered coordinate space across the tangential dimension of cortex.

References and Notes

1. J. M. Allman, J. F. Baker, W. T. Newsome, S. E. Petersen, in *Cortical Sensory Organization*, C. N. Woolsey, Ed. (Humana, Clifton, N.J., 1981), vol. 2, pp. 171–185.
2. D. A. Robinson, in *Basic Mechanisms of Ocular Motility and Their Clinical Implications*, P. Bach-y-Rita and G. Lernerstrand, Eds. (Pergamon, London, 1975), pp. 337–374; P. E. Hallet and A. D. Lightstone, *Vision Res.* **16**, 99 (1976); L. E. Mays and D. L. Sparks, *J. Neurophysiol.* **43**, 207 (1980); R. M. Hansen and A. A. Skavenski, *Vision Res.* **17**, 919 (1977).
3. D. M. MacKay, in *Handbook of Sensory Physiology*, vol. 7, part 3, *Central Processing of Vision Information*, R. Jung, Ed. (Springer-Verlag, Berlin, 1973), pp. 307–331.
4. M. Critchley, *The Parietal Lobes* (Hafner, New York, 1982); G. Ratcliff and G. A. B. Davies-Jones, *Brain* **95**, 49 (1972); R. H. Lamotte and C. Acuna, *Brain Res.* **139**, 309 (1978).
5. R. A. Andersen and V. B. Mountcastle, *J. Neurosci.* **3**, 532 (1983).
6. A. F. Fuchs and D. A. Robinson, *J. Appl. Physiol.* **21**, 1068 (1966).
7. In collecting the data for each spatial gain field, eight replications of retinotopically identical stimuli were delivered at each of the nine eye positions by following a randomized block design. The visually elicited response rates were adjusted for background activity, which often varied with eye position. Conventional linear regression techniques were applied to partition the response variability into components dependent on x and y eye positions and residual "pure error" and "lack-of-fit" components for statistical testing [D. G. Kleinbaum and L. L. Kupper, *Applied Regression Analysis and Other Multivariable Methods* (Duxbury, North Scituate, Mass., 1978); J. Netter and W. Wasserman, *Applied Linear Regression Analysis* (Irwin, Homewood, Ill., 1983).

8. Supported by NIH grant EY 05522, a McKnight Foundation scholars award to R.A.A., a Sloan Foundation fellowship to R.A.A., and NIH postdoctoral training grant NS 07457 to R.M.S. This research was conducted in part by the Clayton Foundation for Research–California Division. R.A.A. is a Clayton Foundation for Research investigator. We thank W. M. Cowan, F. Crick, and S. LeVay for comments on the manuscript.

4 April 1985; accepted 29 July 1985

Molecular Defects in a Human Immunoglobulin κ Chain Deficiency

Abstract. *The molecular basis of a human immunoglobulin deficiency characterized by the complete absence of κ chains has been investigated by nucleotide sequence analyses of a patient's κ constant region (C_κ) genes. Both of his C_κ genes had a single point mutation, resulting in the loss of the invariant tryptophan from one allele and of an invariant cysteine from the other allele. These results indicate that neither of the patient's C_κ alleles encoded a κ chain that could form a stable intradomain disulfide bond, although peculiarities in the expression of κ chains in the patient's family suggest that other factors may be involved.*

JANET STAVNEZER-NORDGREN*
OLGA KEKISH
Molecular Biology and Virology Program, Sloan-Kettering Institute, New York 10021
BEN J. M. ZEGERS
Department of Immunology, University Children's Hospital, Nieuwe Gracht 137, Utrecht, Netherlands

*Present address: Department of Molecular Genetics and Microbiology, University of Massachusetts School of Medicine, Worcester 01605.

One case of complete absence of immunoglobulin (Ig) κ chains (*1*) and a few cases of reduced expression of κ chains have been reported in humans (*2*). We have studied the molecular basis of the absence of κ chains in the completely κ-deficient individual. As B lymphocytes bearing κ chains could not be detected in this individual's blood or bone marrow, the defect did not seem to be due to an inability of κ-expressing lymphocytes to mature to a secreting stage (*1*). We hypothesized that the cause of the deficiency could be deletions of or mutations in genes coding for Ig κ chains; however, defects could also be in other genes that affect the expression of κ chains, since serum from the κ-deficient individual's sister contained a very low amount of κ chains, and sera from his parents and other sibling had approximately normal amounts of κ chains (*1*). We have investigated the cause of this case of κ chain deficiency by nucleotide sequence analysis of both of the κ constant region (C_κ) genes from the patient. Each C_κ gene had a different single point mutation, which resulted in the loss of the invariant tryptophan at amino acid position 148 from one allele and one of the two invariant cysteines (at position 194) from the other allele, so that neither of his C_κ domains should be able to form stable intradomain disulfide bonds.

To search for any gross rearrangements or large deletions in the patient's Ig κ genes, genomic DNA from blood leukocytes (more than 95 percent of which do not produce Ig) from the patient and his parents was analyzed by DNA blotting experiments (*3*). No differences were detected among restriction fragments containing Ig C_κ or J_κ (J, joining) genes in the patient, his parents, and in normal human placenta, with three different restriction enzymes (Bam HI, Eco RI, and Bgl II). To determine

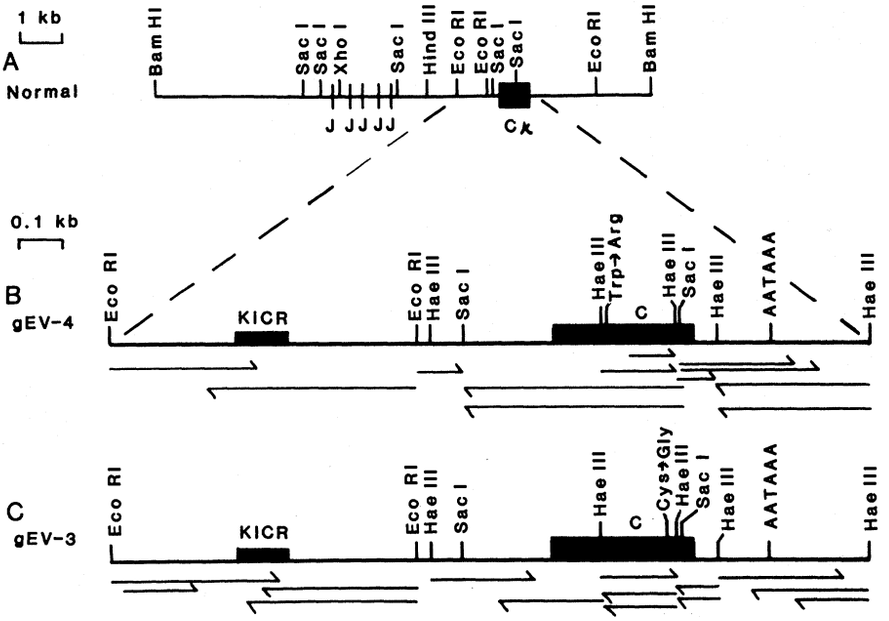

Fig. 1. Restriction enzyme maps of the germline J_κ-C_κ segment and DNA sequencing strategy. (A) Map of J_κ-C_κ segment in normal humans (*7*) and in the κ-deficient human. Mapping of the segment from the patient was done by blotting of genomic DNA and by restriction enzyme digestion of cloned DNA segments. (B) Expanded map of DNA segment containing the C_κ gene and conserved region (KICR) present in one J_κ-C_κ allele cloned from the κ-deficient human (gEV-4). The location of the point mutation at nucleotide position 1150, causing the conversion of Trp to Arg at amino acid residue 148, is indicated. Each arrow indicates the region sequenced in a separate dideoxynucleotide sequencing region, usually performed on different M13 clones. (C) Map and sequencing strategy (arrows) for the second C_κ segment cloned from the patient (gEV-3), containing a mutation at nucleotide position 1288, which converted the Cys at amino acid position 194 to Gly.

whether the patient had genes encoding the variable (V) regions of κ chains, we annealed blots of genomic DNA from two B lymphoblastoid cell lines (LCL's) from the patient, produced by transformation with Epstein-Barr virus (*4*), with a DNA fragment encoding a human V_κ gene (HK101) (*5*). No differences among the V_κ genes in these cells, in LCL's from a normal individual, and cells from a normal placenta were detected. To search for any abnormality in the genes encoding λ chains which could cause λ genes to be expressed rather than κ genes, a blot of leukocyte DNA's from the patient and his parents was annealed with a human C_λ gene segment (*6*). No differences from normal human placenta were detected.

Because genomic DNA blotting experiments would not detect small deletions or sequence alterations, it was necessary to clone and sequence the patient's κ chain genes. We reasoned that the C_κ genes were probably the site of the mutations because humans have a single C_κ gene, whereas there are 5 J_κ and at least 25 to 50 V_κ gene segments (*5, 7, 8*). It would be unlikely that all of the J_κ or V_κ gene segments were mutated.

To obtain the germline J_κ-C_κ gene segment from the patient, Bam HI fragments, 8 to 15 kilobase pairs (kb) long, were cloned from his leukocyte DNA in the λ phage vector, L47.1 (*9*). Three isolates (gEV-2, gEV-3, and gEV-4) containing the J_κ-C_κ Bam HI fragment were obtained from 1×10^6 recombinant phages. The 11.4-kb Bam HI inserts from these phages and the 11.4-kb Bam HI insert containing the normal human J_κ-C_κ gene segment appeared identical

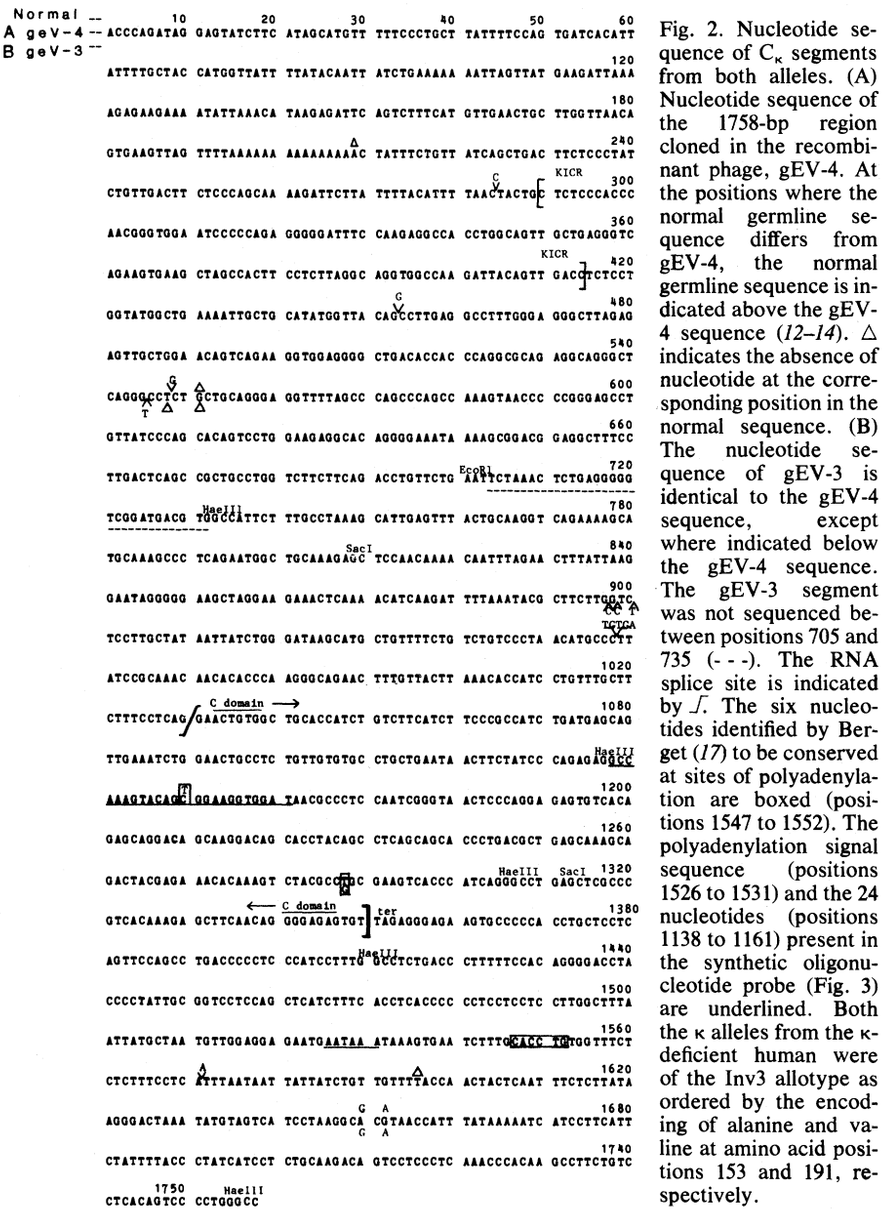

Fig. 2. Nucleotide sequence of C_κ segments from both alleles. (A) Nucleotide sequence of the 1758-bp region cloned in the recombinant phage, gEV-4. At the positions where the normal germline sequence differs from gEV-4, the normal germline sequence is indicated above the gEV-4 sequence (*12–14*). △ indicates the absence of nucleotide at the corresponding position in the normal sequence. (B) The nucleotide sequence of gEV-3 is identical to the gEV-4 sequence, except where indicated below the gEV-4 sequence. The gEV-3 segment was not sequenced between positions 705 and 735 (- - -). The RNA splice site is indicated by ⌐. The six nucleotides identified by Berget (*17*) to be conserved at sites of polyadenylation are boxed (positions 1547 to 1552). The polyadenylation signal sequence (positions 1526 to 1531) and the 24 nucleotides (positions 1138 to 1161) present in the synthetic oligonucleotide probe (Fig. 3) are underlined. Both the κ alleles from the κ-deficient human were of the Inv3 allotype as ordered by the encoding of alanine and valine at amino acid positions 153 and 191, respectively.

when digested with Eco RI, Sac I, Xho I, and Hind III. Figure 1A shows a map of the germline J_κ-C_κ allele (*8*).

The nucleotide sequence of the C_κ gene and flanking regions from gEV-4 was determined by subcloning specific restriction fragments into M13 phage (mp8, 9, 10, and 11) (*10*), and sequencing by the dideoxynucleotide chain termination method (*11*). Figure 1B is a diagram of the strategy and the region of gEV-4 that was sequenced. Figure 2A shows the sequence. Only a few nucleotides differed between the gEV-4 sequence and the corresponding 1760 nucleotides from the normal germline J_κ-C_κ segment (*12–14*). Within the C_κ coding region, at position 1150 in Fig. 2, the T present in the normal sequence (*12*) has been replaced by a C, resulting in the conversion of Trp at amino acid position 148 to Arg. This Trp is invariant in all normal C and V regions domains (at the corresponding amino acid position 35 or 36) from both heavy (H) and light (L) chains from all species studied, apparently because it shields the intradomain disulfide bond, and is thus required for a stable intradomain disulfide bond and proper folding of the Ig domains (*15*). The presence of this point mutation may explain why one of the patient's C_κ alleles is nonfunctional. In addition to this mutation, we found an addition or subtraction of a single nucleotide and a deletion of five nucleotides in the 705–base pair (bp) Eco RI fragment located 5′ to the C_κ gene (positions 209, 285, 453, 548, 551, and 958) (Fig. 2A); in these positions the sequence differed from that published by Emorine *et al.* (*13*) and unpublished results of Kuehl (*14*). None of these differences were located within the 125-bp conserved region (KICR), which seems to be a transcriptional activator (*13, 16*) (Fig. 2). Four other changes located 3′ to the polyadenylation signal sequence AATAAA (positions 1526 to 1531) of the C gene are a loss of one nucleotide (position 1571), an addition of one nucleotide (position 1596), and an interchange of two nucleotides (positions 1650 and 1652). None of these changes should cause the κ deficiency, because they are not near splice junctions nor within regions that seem necessary for polyadenylation (*17, 18*).

We then determined whether the two other J_κ-C_κ gene segments cloned from the κ-deficient human also had the T to C transition within the codon for the invariant Trp or differed and were from the other κ allele: DNA from the three recombinant phages was blotted and hybridized with a synthetic oligonucleotide probe complementary to the C_κ gene, with the mutated nucleotide of gEV-4 as a central nucleotide. The 24 nucleotides present in the probe are underlined (solid line) in Fig. 2A (positions 1138 to 1161). DNA from one of the two other clones, gEV-3, hybridized less well than DNA from clone gEV-4 did (lanes 3 and 4 in Fig. 3). Hae III fragments from the 2.7-kb Eco RI fragment containing the gEV-3 C_κ gene were subcloned into mp9 and 10 (Fig. 1C) and sequenced (Fig. 2B). The C_κ gene segment in gEV-3 contained the invariant Trp, but had a different point mutation within the C_κ-coding region. A G replaced the T at nucleotide position 1288, converting the invariant cysteine (Cys) at amino acid position 194 to glycine (Gly). Since this Cys is utilized in the formation of the intradomain disulfide bond, this mutation would prevent the correct folding of any κ chain produced from this C gene. As in gEV-4, the remainder of the region from this allele that was sequenced was essentially identical to that present in a normal human, except for small changes in regions that should not affect the function of the C_κ gene. The sequence of the 705-bp Eco RI fragment located 5′ to the C_κ coding region was identical to the sequence of this fragment in a normal human (*13, 14*), except for five single nucleotide insertions or deletions (Fig. 2B). None of these alterations occurred within the 125-bp conserved region within this fragment. Three of these differences were also present in gEV-4 (positions 209, 285, and 453), but those at positions 545 and 548 occurred only in gEV-3. In the region of the intervening sequence located 3′ to the 705-bp Eco RI fragment, three single nucleotide insertions relative to the normal germline sequence (*12*) were identified (positions 897, 899, and 900). In the region 3′ to the site of polyadenylation, which probably occurs at position 1547 (*17, 18*), two single nucleotide differences (also seen in gEV-4) occurred at positions 1571 and 1596.

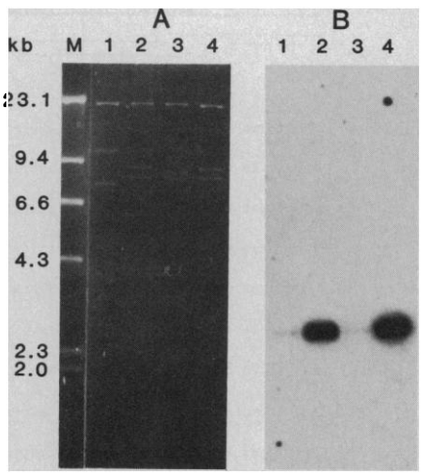

Fig. 3. (A) Agarose gel and (B) blot of DNA from recombinant λ phage containing J_κ-C_κ segments. The blot was annealed with a ^{32}P-labeled oligonucleotide containing the mutated nucleotide present in the gEV-4 C_κ gene. Lanes 1 to 4 contain 7 ng of phage DNA, digested with Eco RI. Lane 1 contains DNA from phage with an insert of the normal J_κ-C_κ segment (*12*). Lanes 2 to 4 contain DNA from phage with inserts cloned from the κ-deficient human: lane 2, gEV-2; lane 3, gEV-3; lane 4, gEV-4. Lane M contains λ phage DNA digested with Hind III. The sizes of the fragments (in kilobase pairs) are indicated. The blot was annealed with 100×10^6 count/min of oligonucleotide (100 to 200 ng), labeled with ^{32}P (by polynucleotide kinase), in a solution containing 50 percent formamide, 900 m*M* NaCl, 90 m*M* sodium citrate, 0.6 m*M* disodium EDTA, 1 mg yeast RNA per milliliter, 0.1 mg *Escherichia coli* DNA per milliliter, and 0.02 percent each of bovine serum albumin, Ficoll, and polyvinyl pyrrolidine for 4 days at 42°C. The blot was washed in a mixture of 0.1 percent sodium dodecyl sulfate and 2× SSPE (SSPE = 150 m*M* NaCl, 1 m*M* disodium EDTA, and 10 m*M* phosphate, *p*H 6.8) at room temperature, then in 0.1× SSPE at 50°C for 1.5 hours, with a final wash in 0.1× SSPE at 56°C for 30 minutes. The blot was exposed to XAR film for 7 days. The 2.7-kb fragments containing the C_κ gene detected by the oligonucleotide probe do not show in the photo of the ethidium bromide–stained gel (A) because of the small amount of phage DNA loaded.

The complete lack of κ chains within this individual is apparently explained by a single different point mutation in each of his C_κ alleles, each of which mutates an amino acid required for formation of the intradomain disulfide bond. These mutated C_κ alleles were probably inherited from his parents and not caused by a mutation occurring during formation of the embryo, because an older sibling had very low levels of κ chain expression (*1*). This finding and the virtually normal κ to λ ratio in the Ig's of his parents (*1*) lead to the conclusion that additional genes or environmental factors may influence the expression of κ genes in this family. Furthermore, we would have expected that the two mutations would have a similar phenotype in the heterozygous form, each reducing the probability of producing a functional κ chain by a factor of 2. Additional studies of κ genes in the parents are required to address this question.

The only known example of a genetic κ-deficiency in a nonhuman mammal is found in the Basilea strain of rabbits (*19*). These rabbits express small amounts of a κ chain whose C domain has lost the Cys normally utilized in the formation of a disulfide bond between the V and C domains of rabbit κ chains (*20*). Although rabbits of other strains also express this same C_κ domain, it constitutes only a small portion of their κ chains.

For an unknown reason κ chains containing the Cys required for forming interdomain disulfide bonds are not expressed in the Basilea strain of rabbits (*20*).

Only a few cases of κ deficiency in humans have been reported, perhaps because κ deficiency does not have a drastic effect on the health of the individual—λ chains seem able to substitute effectively. The κ-deficient patient's immune response to a variety of antigens was normal (*1*). Furthermore, mice made κ-deficient by injection of antibodies to κ since birth mounted normal secondary, but defective primary, responses, suggesting that λ chains can substitute for κ chains after diversification by somatic mutation (*21*).

References and Notes

1. B. J. M. Zegers *et al.*, *New Engl. J. Med.* **294**, 1026 (1976).
2. G. M. Bernier, J. R. Gunderman, F. B. Ruymann, *Blood* **40**, 795 (1972); S. Barundun, A. Morell, F. Skvaril, A. Oberdorfer, *ibid.* **47**, 79 (1976).
3. E. M. Southern, *J. Mol. Biol.* **98**, 503 (1975); J. Stavnezer, K. B. Marcu, S. Sirlin, B. Alhadeff, U. Hamerling, *Mol. Cell. Biol.* **2**, 1002 (1982).
4. E. Henderson, G. Miller, J. Robinson, L. Heston, *Virology* **76**, 152 (1977); J. Stavnezer *et al.*, *Nucleic Acids Res.* **13**, 3495 (1985).
5. D. L. Bentley and T. J. Rabbitts, *Nature (London)* **288**, 730 (1980).
6. P. A. Hieter, S. J. Korsmeyer, T. A. Waldmann, P. Leder, *ibid.* **290**, 368 (1981).
7. P. A. Hieter, J. V. Maizel, Jr., P. Leder, *J. Biol. Chem.* **257**, 1516 (1982).
8. D. L. Bentley, *Nature (London)* **307**, 77 (1984); H.-G. Klobeck, A. Solomon, H. G. Zachau, *ibid.* **309**, 73 (1984).
9. W. A. M. Loenen and W. J. Brammar, *Gene* **20**, 249 (1980).
10. J. Messing and J. Vieira, *ibid.* **19**, 269 (1982); J. Messing, *Methods Enzymol.* **101**, 20 (1983).
11. F. Sanger, S. Nicklen, A. Coulson, *Proc. Natl. Acad. Sci. U.S.A.* **74**, 5463 (1977); A. M. Maxam and W. Gilbert, *Methods Enzymol.* **65**, 499 (1980); A. T. Bankier and B. G. Barrell, *Techniques in Life Sciences, Nucleic Acid Biochemistry* (Elsevier, Dublin, 1983), vol. B508, pp. 1–34.
12. P. A. Hieter, E. E. Max, J. G. Seidman, J. V. Maizel, Jr., P. Leder, *Cell* **22**, 197 (1980).
13. L. Emorine, M. Kuehl, L. Weir, P. Leder, E. Max, *Nature (London)* **304**, 447 (1983).
14. W. M. Kuehl, personal communication.
15. D. Beale and A. Feinstein, *Q. Rev. Biophys.* **9**, 135 (1976); E. A. Kabat, T. T. Wu, H. Bilofsky, M. Reid-Miller, H. Perry, *Sequences of Proteins of Immunological Interest* (National Institutes of Health, Bethesda, Md., 1983).
16. D. Picard and W. Schaffner, *Nature (London)* **307**, 80 (1984); C. Queen and J. Stafford, *Mol. Cell. Biol.* **4**, 1042 (1984).
17. S. M. Berget, *Nature (London)* **309**, 179 (1984).
18. M. A. McDevitt, M. J. Imperiale, H. Ali, J. R. Nevins, *Cell* **37**, 993 (1984).
19. A. S. Kelus and S. Weiss, *Nature (London)* **265**, 156 (1977).
20. K. E. Bernstein, E. Lamoyi, N. McCartney-Francis, R. G. Mage, *J. Exp. Med.* **159**, 635 (1984).
21. S. Weiss, K. Lehmann, W. C. Rashke, M. Cohn, *Proc. Natl. Acad. Sci. U.S.A.* **81**, 211 (1984).

22. We thank J. M. Bishop for suggesting the studies of the κ-deficient patient; J. van der Laag for the clinical assessment of the patient; P. Leder, T. Rabbitts, and S. Korsmeyer for recombinant DNA probes; P. Model and S. Lukin for synthesis of the oligonucleotide probe; S. Sirlin for excellent technical assistance; and M. Siniscalco and M. Purrello for critical reading of the manuscript. Supported by a National Institutes of Health grant (AI17558) and by a Basil O'Connor grant (5-255) from the March of Dimes Birth Defects Foundation.

12 April 1985; accepted 3 September 1985

Patterns of Growth Hormone–Releasing Factor and Somatostatin Secretion into the Hypophysial-Portal Circulation of the Rat

Abstract. *The interrelation between the secretion of two hypophysiotropic peptides, growth hormone–releasing factor (GRF) and somatostatin (SRIF), in the generation of episodic growth hormone (GH) secretion was inferred from direct measurements of immunoreactive GRF and immunoreactive SRIF concentrations in the hypophysial-portal plasma of the rat. Secretion of immunoreactive GRF was found to be episodic, with maximal concentrations present during periods of expected GH secretory episodes. Secretion of immunoreactive GRF was accompanied by a moderate reduction in portal plasma levels of immunoreactive SRIF. Passive immunoneutralization of SRIF was associated with increased concentrations of immunoreactive GRF in hypophysial-portal plasma. On the basis of these observations, it appears that each GH secretory episode is initiated by pulsatile secretion of immunoreactive GRF into the portal circulation, which is preceded by or is concurrent with a moderate reduction of inhibitory tone provided by portal immunoreactive SRIF. These experiments provide direct insights into central and adenohypophysial mechanisms by which GRF and SRIF interact to generate episodic secretion of GH.*

PAUL M. PLOTSKY
WYLIE VALE
Clayton Foundation Laboratories for Peptide Biology, Salk Institute, La Jolla, California 92037

Spontaneous secretion of growth hormone (GH) in the rat (*1*) and other species (*2*) is characterized by episodic, high-amplitude bursts separated by troughs of low-level secretion throughout each 24-hour period. The hypothalamic regulation of GH secretion appears to be mediated by two peptides, a recently identified stimulatory factor, growth hormone–releasing factor (GRF) (*3*), and an inhibitory peptide, somatostatin (SRIF) (*4*). These factors reach the anterior pituitary gland via the hypophysial-portal circulation after release from nerve endings in the zona externa of the median eminence (*5*). The central and adenohypophysial mechanisms by which GRF and SRIF interact to generate episodic secretion of GH are not well understood.

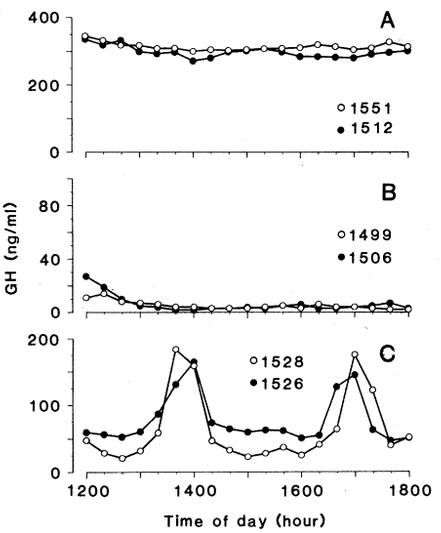

Fig. 1. Representative examples of GH secretory patterns in rats anesthetized with (A) pentobarbital, (B) urethan, or (C) ketamine: xylazine (see text for details).

Removal of the inhibitory influence of SRIF by passive immunoneutralization (*6*), electrolytic lesion of regions rich in SRIF perikarya (*7*), or hypothalamic cuts (*8*) increases the trough levels of GH. Withdrawal of exogenous SRIF is accompanied by rebound secretion of GH (*9*). Thus SRIF is a component of the dynamic GH release mechanism. Analyses of hypothalamic secretion of immunoreactive SRIF, based on the use of intracerebral push-pull perfusion sampling (*10*) and hypophysial-portal collection (*11*) techniques, have failed to convincingly establish the secretory dynamics of endogenous SRIF. To our knowledge, neither in vitro nor in vivo studies of GRF secretion have been reported. However, Wehrenberg *et al.* and others (*12*) have demonstrated blockade of episodic, but not of trough, GH secretion by passive immunoneutralization with specific antisera to synthetic GRF. This body of observations has led to the development of several hypothetical models of the GH regulatory process (*13*).

Our experiments were designed to probe the nature of hypophysiotropic regulation of GH secretion from the adenohypophysis. Participation of GRF and SRIF in the generation of episodic GH secretory patterns was inferred from changes in the hypophysial-portal concentrations of these peptides. Male rats (325 to 375 g) of the Sprague-Dawley strain (Charles River) were anesthetized with urethan (1.1 g per kilogram of body weight, intraperitoneally), pentobarbital (30 mg/kg intraperitoneally), or a mixture