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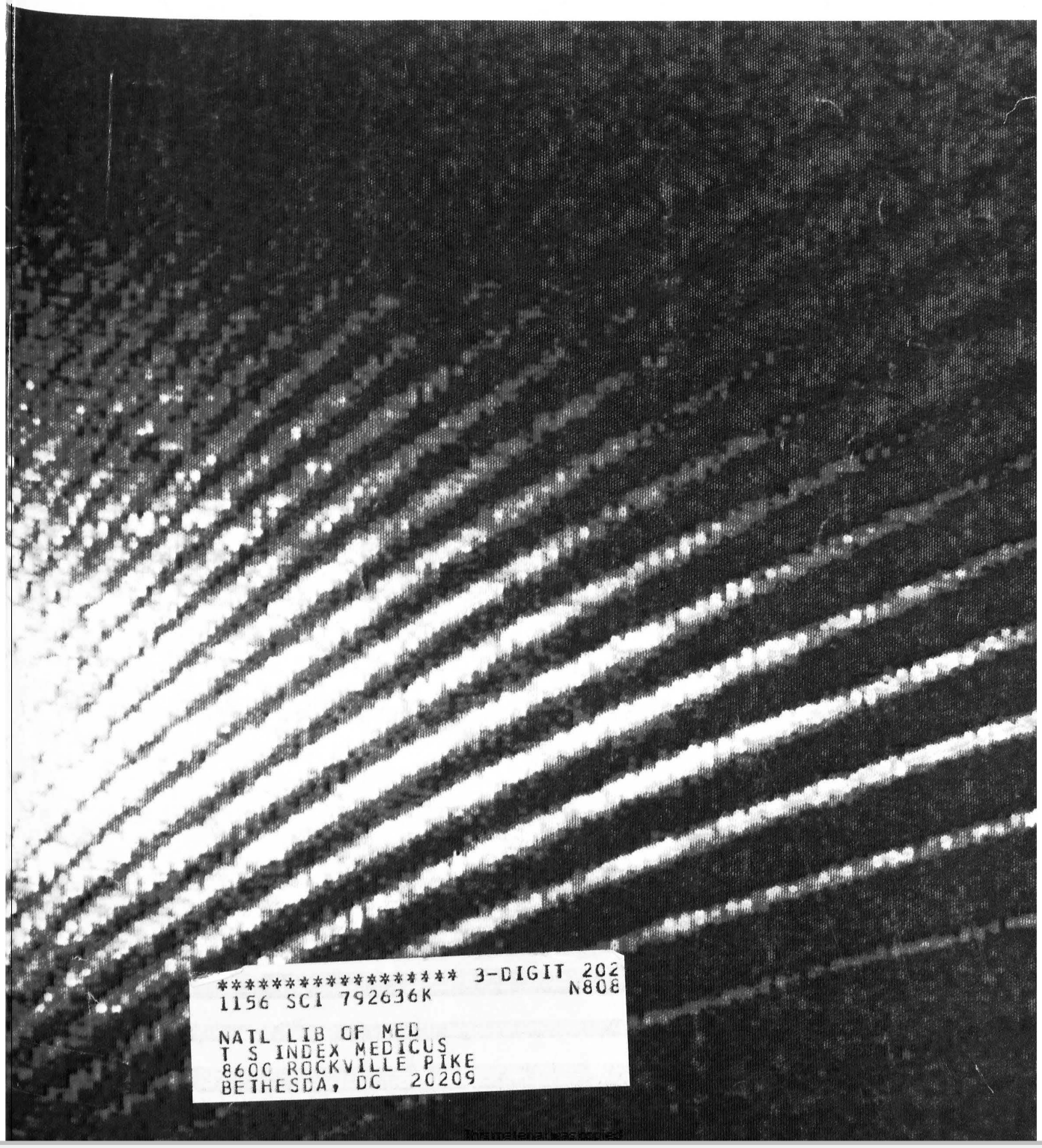

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COVER

Power as observed in solar 5-minute oscillations with frequency ν (from about 1.5 mHz at bottom to 5.7 mHz at top and degree l (from about 7 on left to 170 on right). The narrow ridges of concentrated power (shown by the lighter tones) corresponds to theoretically predicted acoustic resonances in the sun. Analysis of observed frequencies permits study of the structure and dynamics of the solar interior. See page 923. [T. L. Duvall, Jr., and J. W. Harvey, National Solar Observatory, P.O. Box 26732, Tucson, Arizona 85726]

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To: Universal Science Foundation
Planet Utopia
Galaxy 7,073,216

From: Intergalactic Cultural Anthropology Expedition
Sections IV and XXI

Re: Anomalous Behavior Patterns

The expedition to examine subcultures and behavioral patterns on Planet Earth has uncovered an anomaly that defies explanation by the rational principles and Cartesian logic of our own planet. Sections IV and XXI traveled independently in separate cruise missiles and randomly selected inhabitants for analysis by our noninvasive probes; that is, acoustical eavesdropping and quantitative three-dimensional gossip.

At 3:00 p.m. Earth Time on 4 August, Section IV located an individual with a red face speaking into a telephone at the 10^3-decibel level. The subject was using arcane linguistic techniques with multisyllable words such as "nincompoop" and "incompetent" occasionally interspersed with four-letter words not available in captured dictionaries. This species, which Section IV calls "Author," was complaining bitterly to something called *The Journal* that his manuscript had received no decision in 3 weeks despite (i) it represented better work than had ever appeared in that journal for the last decade and (ii) it was easily the best of his 176 papers, none of which had been treated so shabbily. It was ascertained that this work had taken 2 years to complete, 3 months to write up, and 1.5 months to be criticized by colleagues of the Author before being sent to *The Journal*. At 3:37 p.m., Section IV moved on to study behavior of one horse, two bullfinches, and a garter snake, all of which behaved in a classical and rational Cartesian manner.

At 4:00 p.m. on 4 August, Section XXI located an individual with a red face speaking into a telephone at the 10^{-3}-decibel level using multisyllable words such as "impossible" and "inconceivable" occasionally broken by signs, groans, and anguished looks at the ceiling. This species, which Section XXI calls "Referee," was apologizing to something called *The Journal* that (i) the manuscript that he had received for review had only recently arrived, having been delayed in the mails; (ii) he had in fact been studying the manuscript for weeks; and (iii) it had come during a period when he was out of the country, writing a grant, lecturing to 300 students, and lying flat on his back in the hospital being fed intravenously. He promised that the manuscript would be put in the mail "tomorrow" and complained that it was unreasonable of *The Journal* to expect a busy Referee such as he was to review a manuscript in less than 3 weeks. Section XXI was unable to obtain a definition of the word "tomorrow" before it moved on to study the viscosity of rush-hour traffic.

The anomaly in the case was not recognized until the two sections received laboratory reports of their remote-sensing DNA-sequencing determinations and optical surface imagery. The former indicated identical DNA sequences for the two species and optical photographs revealed identical clothing and facial characteristics. The sections concluded that it was theoretically astounding, but experimentally conclusive, that both expeditionary units had observed the same individual. No explanation for the subject's behavior could be suggested until Professor X173 discovered that there were two hemispheres of the brain of *Homo sapiens*. We conclude that a single body houses both species, but that the Author species uses the left hemisphere and the Referee species the right hemisphere, and there is no cross-correlative system. Professor X173 predicts that such split personalities will create wars, famines, and two types of Coca-Cola.

—DANIEL E. KOSHLAND, JR.

Amplification of a Novel v-*erb*B–Related Gene in a Human Mammary Carcinoma

Abstract. *The cellular gene encoding the receptor for epidermal growth factor (EGF) has considerable homology to the oncogene of avian erythroblastosis virus. In a human mammary carcinoma, a DNA sequence was identified that is related to v-*erb*B but amplified in a manner that appeared to distinguish it from the gene for the EGF receptor. Molecular cloning of this DNA segment and nucleotide sequence analysis revealed the presence of two putative exons in a DNA segment whose predicted amino acid sequence was closely related to, but different from, the corresponding sequence of the* erb*B/EGF receptor. Moreover, this DNA segment identified a 5-kilobase transcript distinct from the transcripts of the EGF receptor gene. Thus, a new member of the tyrosine kinase proto-oncogene family has been identified on the basis of its amplification in a human mammary carcinoma.*

C. Richter King
Matthias H. Kraus
Stuart A. Aaronson
Laboratory of Cellular and Molecular Biology, National Cancer Institute, Bethesda, Maryland 20205

The oncogenes of the acute transforming retroviruses have counterparts, designated proto-oncogenes, that are conserved within the human genome (*1*). The human *sis* proto-oncogene encodes one major polypeptide chain of platelet-derived growth factor (PDGF) (*2*), and the *erb*B proto-oncogene appears to encode the receptor for epidermal growth factor (EGF) (*3*). A number of other proto-oncogenes, like *erb*B, share nucleotide sequence homology with the tyrosine kinase–encoding *src* gene (*4*). The fact that cellular receptors for several growth factors or hormones, including the EGF receptor, possess this enzymatic activity suggests that other proto-oncogenes may encode growth factor receptors as well.

Genetic alterations affecting proto-oncogenes of the tyrosine kinase family can play a role in spontaneous tumor development. A specific translocation affecting the c-*abl* locus, for example, is associated with chronic myelogenous leukemia (*5*). Several recent studies have also documented amplification or rearrangement of the gene for the EGF receptor in certain human tumors (*6*) or tumor cell lines (*7*). We now report the detection and partial isolation of a gene that is a new member of the tyrosine kinase family and is amplified in a human mammary carcinoma. This gene is closely related to, but distinct from, the EGF receptor gene.

The identification of additional members of some proto-oncogene families has emerged from findings of related sequences amplified sufficiently in a particular tumor to allow detection (*8*). Because of our interest in genes coding for growth factor receptors, we used the v-*erb*B gene to probe for related genes that might be candidates for other receptor coding sequences. We selected moderate stringency hybridization conditions under which different oncogenes of the tyrosine family did not cross-hybridize. Thus, any gene detected might be expected to have a closer relationship to v-*erb*B than to other members of the tyrosine kinase family.

DNA prepared from tissue of a human mammary carcinoma, MAC117, showed a pattern of hybridization (Fig. 1A) that differed both from that observed with DNA of normal human placenta and from that observed with the A431 squamous-cell carcinoma line, which contains amplified EGF receptor genes (*7*). In A431 DNA, four Eco RI fragments were detected that had increased signal intensities compared to those of corresponding fragments in placenta DNA (Fig. 1A). In contrast, MAC117 DNA contained a single 6-kilobase pair (kbp) fragment, which appeared to be amplified compared to corresponding fragments observed in both A431 and placenta DNA's (Fig. 1A). These findings were consistent with the possibility that the MAC117 tumor contained an amplified DNA sequence related to, but distinct from, the cellular *erb*B proto-oncogene.

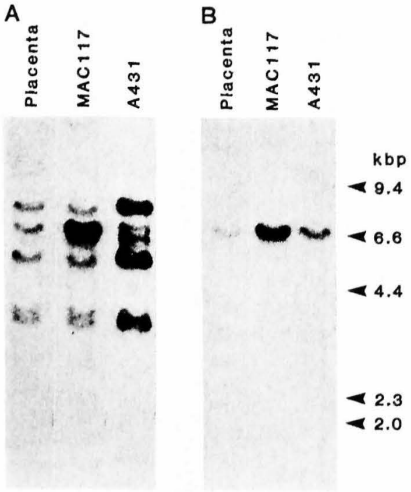

Fig. 1. Detection of v-*erb*B– and pMAC 117–specific gene fragments in normal human placenta, A431 cells, or human mammary carcinoma MAC117. DNA (15 μg) was cleaved with Eco RI, separated by electrophoresis in agarose gels, and transferred to nitrocellulose paper (*18*). Hybridization to the ^{32}P-labeled probe (*20*) was conducted in a solution of 40 percent formamide, 0.75*M* NaCl, 0.075*M* sodium citrate, at 42°C (*19*). The v-*erb*B probe (A) was a mixture of the 0.5-kbp Bam HI–Bam HI fragment and 0.5-kbp Bam HI–Eco RI fragment of avian erythroblastosis proviral DNA. The pMAC117 probe (B) was a 1-kbp Bgl I–Bam HI fragment. After hybridization, the blots were washed first in 0.3*M* NaCl plus 0.03*M* sodium citrate at room temperature, and then in 0.015*M* NaCl, 0.0015*M* sodium citrate, and 0.1 percent sodium dodecyl sulfate at 42°C (A) or at 52°C (B). Hybridization was detected by autoradiography.

To clone the 6-kbp fragment, we digested DNA from MAC117 with Eco RI, ligated it into bacteriophage λgtWES, packaged it in vitro, and transferred it to *Escherichia coli* strain BNN45 by infection. A library of 4×10^5 bacteriophages was screened by plaque hybridization with radioactive v-*erb*B DNA. Ten of 14 hybridizing phages contained a 6-kbp Eco RI fragment. Figure 2 shows the physical map of one of these phages, λMAC117, and pMAC117, a pUC12 subclone containing a 2-kbp Bam HI fragment of λMAC117 that hybridized with v-*erb*B probes. The region of pMAC117 to which v-*erb*B hybridized most intensely was flanked by Acc I and Nco I sites. Human repetitive sequences were also localized (Fig. 2, region demarcated by arrows).

By digestion of pMAC117 with Bgl I and Bam HI, it was possible to generate a single-copy probe homologous to v-*erb*B. This probe detected a 6-kb Eco RI fragment that was amplified in MAC117 DNA and possibly increased in A431 cellular DNA relative to normal DNA (Fig. 1B). The sizes of the fragments corresponded to the amplified 6-kb Eco RI fragment detected in MAC117 DNA by means of v-*erb*B (Fig. 1A). Hybridization to Southern blots containing serial dilutions of MAC117 genomic DNA indicated an approximate amplification of 5- to 10-fold when compared to human placenta DNA.

The nucleotide sequence of the portion of pMAC117 located between the Nco I and Acc I sites contained two regions of nucleotide sequence homologous to v-*erb*B separated by 122 nucleotides (Fig. 3). These regions shared 69 percent nucleotide sequence identity with both the v-*erb*B and the human EGF receptor gene. The predicted amino

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