that the outstanding objection to the specification be withdrawn.

2. The Rejection of Prior Claims 20, 23, 27 and 30 Under The Second Paragraph of Section 112 Is Inapplicable To Corresponding New Claims 80, 83, 87 and 90

Partially reiterating a prior position taken by the Patent Office, the Examiner has objected to Applicant's reference in certain claims to DNA sequence information contained in Figures of the drawing, stating: "Ordinarily claims should not refer to drawings particularly as here where the material referred to can be easily described without resort to drawings". Applicant respectfully disagrees with the Examiner's position and reiterates the remarks set out at pages 11 and 12 of his prior communication responding to the prior Patent Office notation that the DNA sequences of the Figures could "adequately be expressed in words". Applicant again relies on the authority of the decisions of In re Faust, 86 U.S.P.Q. 114, 115 (1943) and Ex parte Squires, 133 U.S.P.Q. 598, 600 (Bd. App. 1961) in support of his position.

Responding to the prior Patent Office suggestion, Applicant has wholly reconstituted Tables V, VI, XIV and XXI as drawing Figures 5-8. The subject DNA sequences thus appear twice in the application as it is presently constituted. As the Examiner will note, Figure 5 spans three full pages, Figure 6 covers five pages, and Figures 7 and 8 each comprehend a full page of information. Applicant respectfully disagrees that this sequence information "can be easily described without resort to drawings" as suggested by the Examiner. It simply cannot be reasonably suggested that there might be a violation of the standards of definiteness

of Section 112 (second paragraph) in Applicant's refraining from setting out the voluminous DNA sequences in the claims, when this same information already appear twice in the specification. Applicant therefore submits that the outstanding rejection of prior claims 20, 23, 27 and 30 may not properly be applied to corresponding new claims 80, 83, 87 and 90.

3. The "Provisional" Rejection of All Claims Under 35 U.S.C. §101 May Not Properly Be Maintained

Reiterating a prior Patent Office position, the Examiner has lodged a "provisional" rejection of all claims under Section 101 based on the presentation of claims of similar scope in Applicant's "parent" patent applications Serial Nos. 582,185 and 655,841. Applicant previously acknowledged with thanks this notation of potential nonconformity with Section 101 and did not contend (as suggested by the Examiner) that the statute would not bar allowance of the same claims in more than one application. Applicant further notes that Serial No. 582,185 has been expressly abandoned and that a provisional election of prosecution of non-overlapping claim 48 is being concurrently made in Serial No. 655,841, with a corresponding cancellation of claims 1-47 therein. Applicant continues to submit, however, that the provisional notation does not provide a present basis for rejection of the claims. It is thus submitted that the outstanding "provisional" rejection be withdrawn.

4. The Rejection of Prior Claims 14, 15, 17-19, 21, 23, 24, 25, 28, 31-34, 36, 58, 61-66 and 69-71 Under The First Paragraph of Section 112 May Not Properly Be Applied to Corresponding New Claims 73, 74, 77-79, 81, 83, 84, 85, 88, 91, 92, 93, 96 and 103

It was the Examiner's position that Applicant's use of the term "fragments thereof" in reference to claimed DNA sequence portions and/or his use of the term, "having at least a part of the primary structural conformation and one or more of the biological activities of naturally-occurring erythropoietin" in reference to polypeptides encoded by claimed DNA sequences was not "enabled" by the specification. The Examiner argued that either of these terms allows the claims "to read on proteins and peptides completely unrelated to erythropoietin" and that "those unrelated proteins could possess the common biological activity of being an antigen". Based on this argument, a Section 112 rejection was lodged against 14, 15, 17-19, 21, 22, 24, 25, 28, 31-34, 36, 58, 61-66 and 69-71. Applicant respectfully traverses the Examiner's rejection on such grounds.

Consistent with the substance of the discussions with the Examiner at the interview of March 4, 1987, wherein it was noted by the Examiner that the term "fragments" appeared to introduce a redundancy in claim 14, and notwithstanding Applicant's traversal, Applicant has herewith sought amendment to delete reference to "fragments" from prior independent claims 14 and 58. Corresponding new claims 73 and 103 no longer contain this term. Furthermore, Applicant has sought amendment of prior claims 14 and 17 referring to "biological activity" in a manner providing for recitation of "therapeutic activity" and similar recitation was added to prior claim 34. Corresponding new independent

Claim 96

claims 73, 77 and 96 thus refer to "therapeutic activity" rather than "biological activity".

These amendments have been sought for the purpose of advancing prosecution of the application and without waiver of Applicant's right to pursue claims of the form previously advanced in a duly filed continuing application.

Amendment of the claims is believed to moot the issues raised in the rejection and no rejection may properly be lodged against new claims 73, 74, 77-79, 81, 83, 84, 85, 88, 91, 92, 93, 96 and 103.

5. The Rejection of Prior Claim 35 Under 35 U.S.C. §112, Second Paragraph May Not Properly Be Applied to Corresponding Claim 100

The Examiner has rejected claim 35 with the notation that "use of brackets for indicating different species and strains of erythropoietin DNA sequence is improper since brackets in claims designates excluding the bracketed material". Applicant respectfully disagrees with the Examiner's position and proposes that brackets may properly be a part of a claim and are improper only when used for purposes of an amendment designating the deletion of a portion of a claims which already properly contains bracketed subject matter. In support of this position, applicant cites to 37 C.F.R. §1.121 which provides in pertinent part:

> "(d) Where underlining or brackets are intended to appear in the printed patent or are properly part of the claimed material and are not intended as symbolic of changes in the particular claim, amendment by rewriting in accordance with paragraph (b) of this section shall be prohibited."

302 284

It should be apparent from the above, that the brackets present in claim 100 are not "intended as symbolic of changes" and their use is thus in keeping with all "definiteness" requirements of 35 U.S.C. §112 and no proper basis for rejection exists.

6. The Rejection of Prior Claims 14, 15, 61, 62 and 69 Under 35 U.S.C. §112, First Paragraph, May Not Properly Be Applied To Corresponding Claims 73-76

It was the Examiner's position, based on the disclosures of Walker et al., Techniques In Mol. Biology, Macmillan Pub. Co., N.Y., p. 280 (1983) and Kennell et al., Progr.Nucl.Acid.Res.Mol.Biol., 11, 259-301 (1971)*, that claims 14, 15, 61 and 69 (which refer to DNA hybridization) may be rejected because "the disclosure is enabling only for claims limited [to] the conditions of hybridization". Applicant respectfully disagrees and submits that a reading of the claims in light of the specification reveals that the reference to hybridization is not at all unduly broad. As noted at specification page 22, lines 5-7 and again at specification page 94, lines 19-24, the context of the hybridization event referred to in the claims is specifically correlated to the hybridization conditions illustrated in the specification with respect to the initial isolation of monkey and human erythropoietin-encoding DNA, or more stringent conditions.

Notwithstanding this position, in keeping with the discussions with the Examiner at the interview of March 4, 1987, Applicant has amended claim 73 to refer to hybridiza-

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* Applicant was provided a copy of pages 259 and 293 of this reference. If other portions are relied upon, advice of same is requested.

tion "under stringent conditions". Applicant therefore submits that claims 73-76 are not properly subject to rejection.

7. The Rejection of Prior Claims 14, 17, 18, 21-24, 26, 27, 31-36, 58 and 61-68 Under 35 U.S.C. §103 Based on Sue et al. Considered with Breslow et al. or Woods et al References May Not Properly be Applied to Corresponding Claims 73, 77, 78, 81-84, 86, 87, 91-93, 96, 99-100, 103, 75, 76, 94, 95, 97, 98, 101 and 102

It was the Examiner's position that the disclosures of the Sue et al. reference (P.N.A.S., 80) taken together with the publications by Breslow et al. [P.N.A.S. (USA), 79, pp. 6861-6865 (1982)] and Woods et al. [P.N.A.S. (USA), 79, pp. 5661-5665 (1982)] render the claimed subject matter obvious. The Examiner noted that the Sue et al. publication discloses what were "believed to be" the first 26 amino terminal residues of human erythropoietin and that the Breslow et al. and Woods et al. references disclose cDNA isolation using mixed probe sequences deduced from known amino acid data of blood protein. Acknowledging that the Sue et al. reference incorrectly designates the presence of an asparagine residue rather than a cysteine residue at position 7, the Examiner nonetheless concludes that:

> "It would be "obvious to isolate the human erythropoietin cDNA sequences by utilizing the Sue et al. erythropoietin amino acid sequence data to devise oligonucleotide probes for use in sequencing a cDNA liver library in the manner taught by Breslow et al. or Woods et al. The fact that the erythropoietin 26 amino acid amino terminal peptide sequence of Sue et al. differs from that of erythropoietin by designating Asn instead of Cys at the seven position is patentably irrelevant since it would not interfere with the preparation of oligonucleotide probes."

Applicant respectfully disagrees with the Examiner's position, submits that the Examiner's conclusions concerning preparation of probes based on the Sue et al. reference are in error, and submits, in turn, that the combination of references falls far short of existing legal standards for support of a conclusion of obviousness.

Briefly stated, Applicant did not do what the Examiner suggests could have been done based on the cited references. More significantly, Applicant would not have been able to do what the Examiner suggests could have been done based on the cited references, i.e., prepare a small number of oligonucleotides and probe for erythropoietin-encoding DNA within a relatively small DNA library.

As the Examiner will recall, Applicant succeeded in his discovery of DNA encoding erythropoietin using screening procedures which are themselves submitted to involve patentable advances in the art of DNA hybridization (as set forth in original claim 60 of the application). More specifically, Applicant employed two distinct sets of mixed probes to find the human genomic sequence. A first set consisted of a mixture of 128 20-mers (see specification Table II). The amino acid sequence which formed the basis for construction of the first set of probes is now known to correspond to residues 46-52 of human erythropoietin. Applicant used both the set of 128 20-mers of Table II and a second set of 128 17-mers (See specification Table III, relating to the sequence now known to correspond to erythropoietin residues 86-91) to jointly probe 1,500,000 phage plaques of human genomic library for the human sequence. Three positive clones were isolated. The set of 128 20-mers was thereafter used to successfully screen a 200,000 colony

monkey kidney cDNA library, with only seven positive clones being isolated from the 200,000 screened. Applicant's use of mixed probes for screening a DNA library (and especially a mammalian genomic library) where the message sought was present in low abundancy had been projected as being "impractical" shortly before applicant's successful work. See, Anderson et al., Reference C2, and specification page 8, line 29 through page 9, line 20 and page 96, lines 2-13. As noted at specification page 9, the Anderson et al. reference states in pertinent part:

> "More generally, mixed-sequence oligodeoxy-nucleotide probes have been used to isolate protein genes of unknown sequence from cDNA libraries. Such probes are typically mixtures of 8-32 oligonucleotides, 14-17 nucleotides in length, representing every possible codon combination for a small stretch (5-6 residues) of amino acid sequence. Under stringent hybridization conditions that discriminate against incorrectly base-paired probes, these mixtures are capable of locating specific gene sequences in clone libraries of low-to-moderate complexity. Nevertheless, because of their short length and heterogeneity, mixed probes often lack the specificity required for probing sequences as complex as a mammalian genome. This makes such a method impractical for the isolation of mammalian protein genes when the corresponding mRNAs are unavailable." (Citations omitted.)

Turning now to the "secondary" references, in both the Woods et al. and Breslow et al. procedures, an opportunity to develop multiple probes suitable for use in screening a cDNA (human liver) library arose as the result of prior knowledge of the certain identity of regions of amino acid residues which were specified by relatively "unambiguous" codons. Thus, in the Breslow reference, the mixture of oligonucleotide probes was synthesized which corresponded to a specific Apo-I protein sequence (Gln-Lys-

Lys-Trp-Gln) known to be present in the polypeptide whose encoding DNA was sought. Only a total of 16 different oligonucleotides was needed in order to develop a complete set of 14-mer probes for use in the cDNA library probing procedures. See Figure 1 on page 6862 of the reference. This low number was due to the relative lack of degeneracy among codons for tryptophane (no degeneracy), lysine (2-fold degeneracy), and glutamine (2-fold degeneracy) residues which made up the known sequence. Screening a cDNA library of only 10,000 colonies (provided by the authors of the Woods, et al. reference) Breslow et al. were able to isolate twenty positive clones. It is noteworthy that Apo-I DNA containing clones were thus conspicuously in relatively large abundance in the library. Nonetheless, the reported screening procedure failed to allow isolation of any clone including the full sequence of the Apo-I gene.

In the "two probe", Woods et al. reference, a total of 32 17-mers were needed to develop one complete set of probes corresponding to amino acids 9-14 of the protein sought, and an additional total of 48 17-mers were needed to ensure complete consonance of at least one probe to the DNA sequence encoding residues 78-83 of the desired protein. See Figure 2 on page 5662 of the reference. The ability of Woods, et al. to isolate 32 positive clones from a total of only 50,000 clones screened when hybridizing with one set of probes, and then to isolate 19 of the 32 using the second set, testifies to the relatively high abundance of the message in the library screened. (Once again, no full sequence clone is stated as having been isolated.)

Turning now to the correct sequence of amino acids within the first 26 residues of human erythropoietin, it is