Symposium on Epidermolysis Bullosa: Molecular Biology and Pathology of the Cutaneous Basement Membrane Zone

Jefferson Medical College, Philadelphia, Pennsylvania, October 4 and 5, 1991

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A one-and-one-half-day symposium focusing on the state of investigation of the cutaneous basement membrane zone (BMZ) with special emphasis on epidermolysis bullosa (EB) was held at Jefferson Medical College, Philadelphia, Pennsylvania, October 4 and 5, 1991. The Conference, which was chaired by Dr. Jouni Uitto, Professor and Chairman, Department of Dermatology, Jefferson Medical College, and Dr. Eugene A. Bauer, Professor and Chairman, Department of Dermatology, Stanford University School of Medicine, was opened with welcoming comments from Joseph S. Gonella, M.D., Dean, Jefferson Medical College, and by Lawrence E. Shulman, M.D., Ph.D., Director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases. The participants were also greeted by Ms. Miriam Feder, Executive Director of the Dystrophic Epidermolysis Bullosa Research Association of America.

Epidermolysis bullosa (EB) is a group of perhaps as many as 20 hereditary and acquired diseases of the skin that share the common feature of the formation of blisters and erosions in response to minor trauma [1]. Among the newest information involving this group of diseases was the topic of the keynote address “Of Mice and Men: The Genetics of Epidermolysis Bullosa Simplex,” given by Dr. Elaine Fuchs, Professor of Molecular Genetics and Cell Biology from the Howard Hughes Medical Institute, University of Chicago. Dr. Fuchs discussed the recent work accomplished in her laboratory, in which one form of EB simplex, the herpetiform variety (sometimes called the Dowling-Meara type), was shown to be associated with mutations in the keratin-14 gene [2,3]. Clues that such an abnormality might exist extended from the early observation that clumping of the tonofilaments occurred in association with early blister formation. To approach this question, Dr. Fuchs and her colleagues created a series of transgenic mice into which had been integrated a truncated portion of the keratin-14 gene. The resulting animals and their offspring developed a clinical disease characterized by severe intraepidermal blistering at birth, and ultrastructural evidence for clumping of the tonofilaments in association with blister formation [3]. The severity of the clinical disease appeared to correlate with the degree of disruption of filament formation, as tested in vitro.

To determine the molecular basis of the defect in the keratin filaments, the group has explored the specific mutations in two EB herpetiformis patients. In each of the patients, they found a point mutation in codon 125, which normally encodes an arginine. In one of the patients, the mutation changes the arginine to cysteine; in the other, the change is from arginine to histidine [2]. Although the precise molecular mechanism is as yet unclear, these mutations result in poor keratin filament formation, thus contributing to cell and tissue fragility. Because keratin 14 (encoded by a gene that resides on chromosome 17) combines with keratin 5 (chromosome 12) to form a heterodimeric filament, it would theoretically be possible to find a mutation in keratin 5 as another cause of EB simplex. Although such a mutation has yet to be discovered, two groups have demonstrated strong genetic linkage in different families to chromosome 12q, the physical location of the keratin 5 gene [4,5].

Other speakers and the topics discussed in the conference were as follows.

Jouni Uitto, M.D., Ph.D. (Jefferson Medical College): Molecular Genetics of the Cutaneous Basement Membrane Zone.
Mou-Li Chu, Ph.D. (Jefferson Medical College): Cloning of Novel Collagen Genes in the Skin.
Angela Christiano, Ph.D. (Jefferson Medical College), Toshihiro Tanaka, M.D. (Kyoto University): Molecular Cloning of Human Type VII Collagen.
George Giudice, Ph.D. (Medical College of Wisconsin): Molecular Characterization of Hemidesmosomal Proteins.
Tobias Gedde-Dahl, M.D. (University of Tromso, Norway): Clinical Phenotypes and Genetics of EB.
Leena Bruckner-Tuderman, M.D., Ph.D. (University Hospital, Zurich): Animal Models of EB.
Ervin Epstein, Jr., M.D. (University of California, San Francisco), Peter Humphries, Ph.D. (Trinity College, Dublin), Markku Ryyänen, M.D., Ph.D. (Jefferson Medical College): Linkage Analyses in Families with Dominant EB Simplex.
Robert Knowlton, Ph.D. (Jefferson Medical College), Alain Hovnanian, M.D. (Hôpital Saint-Louis, Paris): Linkage Studies on Dystrophic Forms of EB.

This symposium was sponsored by the Department of Dermatology, Jefferson Medical College, and co-sponsored by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and by the Dystrophic Epidermolysis Bullosa Research Association of America. The meeting was supported in part by USPHS, NIH grant 1R13AR40984-01. This symposium was the first in a series of meetings celebrating the inauguration of the new Blaustein Life Sciences Building of the Thomas Jefferson University.

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Table I. Candidate Genes in Different Forms of 
EB Encoding Structural Components of the Cutaneous 
Basement Membrane Zone

<table>
<thead>
<tr>
<th>Type of EB</th>
<th>Candidate Genes</th>
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<tbody>
<tr>
<td>Simplex</td>
<td>Keratins and other cytoskeletal proteins</td>
</tr>
<tr>
<td></td>
<td>Cell-cell adhesion molecules, β1 integrins</td>
</tr>
<tr>
<td>Junctional</td>
<td>Hemidesmosomal proteins (BPAG1, BPAG2, α6β4 integrin)</td>
</tr>
<tr>
<td></td>
<td>Anchoring filament proteins (niccin/kalinin/epiligrin)</td>
</tr>
<tr>
<td>Dystrophic</td>
<td>Anchoring fibril proteins (type VII collagen)</td>
</tr>
<tr>
<td></td>
<td>Other BMZ structural macromolecules (type IV collagen, laminin, nidogen, HSPG)</td>
</tr>
</tbody>
</table>

Robin Eady, M.D. (St. Thomas’ Hospital, London): Current Status of Prenatal Diagnosis of EB.
Edward Amento, M.D. (Genentech Inc.): Growth Factors for Enhancement of Cellular Wound Healing.

In addition, a total of 27 poster presentations on various aspects of the cutaneous BMZ and EB were displayed throughout the meeting. The following is the summary of the oral and poster presentations.

**MOLECULAR BIOLOGY OF THE CUTANEOUS BASEMENT MEMBRANE ZONE (BMZ)**

The BMZ of the skin consists of a large number of distinct structural macromolecules that form an intricate matrix at the dermal-epidermal interface. It is now apparent that the presence of sufficient quantities of these macromolecules and their discrete intermolecular interactions are necessary for the functional integrity of the BMZ. Thus, a large number of structural genes could potentially serve as candidate genes in various forms of EB (Table I).

Many of the candidate genes are expressed only in the BMZ of stratifying squamous epithelia, i.e., the skin, mucous membranes, and cornea, and the clinical consequences of mutations in these genes are expected to manifest only in these tissues, as seen in EB.

Theoretically, mutations in other BMZ genes, which are more ubiquitously expressed in all basement membranes, such as type IV collagen, laminin, nidogen, and heparan sulfate proteoglycan, could cause a heritable form of EB, provided that these macromolecules harbor skin-specific domains that interact with other cutaneous BMZ components. Furthermore, novel extracellular matrix components, some of which are skin specific, are continually being described. An example of such progress was a report on the cloning of type XVI collagen from a human skin fibroblast library.

The exploration of the structural features of cutaneous BMZ components has been markedly enhanced by molecular cloning, which has facilitated the elucidation of primary sequences and secondary structures of these relatively large proteins. For example, the primary structures of two hemidesmosomal proteins, bullous pemphigoid antigens 1 and 2 (BPAG1 and BPAG2), have been elucidated from complementary and genomic DNA sequences [6–9]. BPAG1 (a 230-kD non-collagenous protein) is the major autoantigen in bullous pemphigoid, whereas BPAG2 (a 180-kD collagenous protein) serves as an autoantigen in some patients with bullous pemphigoid and also in herpetic gestations. The genes for BPAG1 and BPAG2 have been mapped to two different chromosomal loci, 6p and 10q, respectively [9,10], and these two proteins are therefore clearly distinct gene products. No evidence for genetic linkage of BPAG1 or BPAG2 to any heritable form of EB has been obtained as yet and, in fact, these gene loci have been excluded as candidate genes in a large family with EBS [11].

Recent cloning of the human type VII collagen gene, which was accomplished as a collaborative effort between Jeffrey’s and Stanford’s dermatology research units, has allowed elucidation of this protein [12]. Similar cloning of a partial cDNA corresponding to type VII collagen sequences was reported in this conference by a Japanese team from Kyoto University. Type VII collagen, a major component of anchoring fibrils, consists of a large, ~145-kD collagenous domain, which is interrupted by a 31-amino-acid non-collagenous segment in the middle of the triple-helical portion and by several 1–3 amino acid insertions or deletions in the Gly-X-Y repeat. The collagenous domain is flanked by two globular non-collagenous segments. The larger one, also ~145 kD in size, was previously thought to be carboxy-terminal, but has now clearly been shown to be amino-terminal by cDNA sequence analysis and by comparison with peptide sequences. The large amino-terminal domains of type VII collagen associate with other macromolecules within the basement membranes at the dermal-epidermal junction at one end, and with basement membrane-like structures, known as anchoring plaques, at the other end. This association secures the attachment of the basement membrane to the underlying dermis. Thus, mutations in type VII collagen, or in other basement membrane zone components that interact with type VII collagen, could conceivably result in a dystrophic form of EB.

Of particular interest for study of the junctional forms of EB is a large glycoprotein, BM600 (recently re-named as niccin), which was initially recognized by a monoclonal antibody G93 [13]. Niccin consists of three disulfide-linked subunit polypeptides that constitute the ~600-kD protein. This protein has been shown by immunoelectron microscopy to localize to anchoring filaments that traverse the lamina lucida possibly connecting the hemidesmosomal structures to the lamina densa. Recently, two other proteins, kalinin and epiligrin, with similar biochemical features, have been described [14,15]. It is conceivable that these three proteins are indeed the same or closely related members of a family. Thus, niccin/kalinin/epiligrin is a candidate gene in junctional EB, because immunostaining of skin from patients with this form of EB shows attenuation or absence of immunoreactivity, whereas the staining pattern is normal in other forms of EB (see below). It has also been demonstrated that incubation of epidermal keratinocytes with anti-kalinin antibodies results in dissociation of the cells from substrata, suggesting that kalinin serves as an attachment protein for these cells. It should be noted that two other monoclonal antibodies, 19-DEJ and AA3, show negative immunofluorescence staining in essentially all cases with junctional EB. Thus, characterization of the antigens recognized by these antibodies will be crucial for elucidation of the underlying molecular defects in junctional forms of EB.

Another attachment mechanism that may be involved in securing association of basal keratinocytes to the underlying basement membrane involves integrins, a family of cell-surface receptors that mediate cell-cell and cell-matrix interactions. In particular, the α6β4 integrin, which is expressed by epithelial cells, has been shown by immunofluorescence to be present in the cutaneous BMZ, and immunoelectron microscopy has localized this integrin to hemidesmosomal complexes [16,17]. Thus, α6β4 integrins may mediate the attachment of hemidesmosomes to the anchoring filament proteins and, theoretically, functional aberrations in α6β4 integrins could result in fragility of the skin. However, immunofluorescence of skin from different patients with EB has thus far revealed normal staining patterns for integrin epitopes.

**CLINICAL CONSIDERATIONS IN EB: CLINICAL HETEROGENEITY, DIAGNOSIS, AND THERAPY**

The clinical and genetic heterogeneity of EB was emphasized a number of times in the conference, especially in the context of genetic linkage studies. For example, in the case of EB simplex, it is likely that the severity of disease will be correlated with the type of mutations that are ultimately defined. In another example, drawn from analogies with other disorders of connective tissues (e.g., osteogenesis imperfecta), it was postulated that mutations in the collagenous domains of the type VII collagen gene could lead to altered synthesis, secretion, deposition, and/or degradation of this protein with resultant alterations in the anchoring fibrils at the tissue level.

Major advances have been made in the tools available for diagnosis and more precise sub-classification of various forms of EB. This is particularly true in the case of various immunologic probes, the staining patterns of which are correlated with specific types of EB.
In term infants and older individuals, in addition to prenatal diagnosis, the current diagnostic tool is ultrasonic examination. However, the use of specific antibody preparations has become an essential adjunct to accurate diagnosis. Among the several antibody probes used, two such preparations are especially instructive. i) GB3 antibody defines the BM-600 (niccin) protein complex that localizes to the epidermal-dermal junction with immunofluorescence microscopy and to the lower portion of the lamina lucida with immunoelectron microscopy. Staining with the antibody is markedly diminished or absent in the lethal form of recessive junctional EB [19]. ii) LH7.2 monoclonal antibody defines anchoring fibrils and stains the epidermal-dermal junction with immunofluorescence microscopy and resides at the lower portion of the lamina densa and on the ends of the anchoring fibrils with immunoelectron microscopy. Staining with this monoclonal antibody is markedly diminished or absent in recessive dystrophic EB [20].

Prenatal diagnosis is now widely available for kindreds at risk for the disease. All of the basement membrane zone structures of importance for morphologic evaluation are present by the end of the first trimester [21]. The current technique employed for prenatal diagnosis (fetoscopy and skin biopsy) is performed at 16–18 weeks of estimated gestational age. Typically four samples are taken: two for electron microscopy and two for immunofluorescence analysis. The consensus among those attending the conference was that there had been no apparent instances of false-positive or false-negative prenatal diagnosis of EB.

It was suggested that future therapy of the more severe forms of EB (e.g., recessive dystrophic EB) might be prejudiced, at least in part, on factors that enhance wound healing. Several steps in the wound-healing processes represent cell biological target functions for therapeutic intervention: cell proliferation, matrix protein synthesis (e.g., collagens, fibronectin, proteoglycans, etc.), other proteins of the basement membrane zone, synthesis of the matrix metalloproteinases (interstitial collagenase, stromelysin, 72-kDa type IV collagenase, 92-kDa type IV/V collagenase), activation of the matrix metalloproteinases, and expression and function of the tissue inhibitors of metalloproteinases (TIMP-1, TIMP-2). The net effects of these agents at tissue levels are determined by a host of complex interactions, only some of which are currently well understood. Although it is often true that cytokine stimulation of interstitial collagenase is accompanied by a coordinate up-regulation of TIMP-1 expression, this is not uniformly the case. One recently described example of the complexity of the phenomena that might exist at wound-healing sites involves the consequences of the production of the protein products of the gro gene, now known to have an amino acid sequence identical to the melanoma growth stimulatory activity (MGSA) protein. IL-1 induces MGSA/gro protein within 1 h, and MGSA/gro is autoinductive and therefore amplifies its downstream effects. Although IL-1 alone also induces interstitial collagenase expression in vitro over a 16–20-h period, the combination of MGSA/gro plus IL-1 produces a net decrease in collagenase activity. It is now clear that, despite the up-regulation of collagenase protein synthesis by IL-1, the net decrease in collagenase activity is due to induction of TIMP-1 expression that in turn results in inhibition of collagenase activity.

A number of growth factors and cytokines might be considered in altering the wound-healing response. In particular, in addition to modulation of the migratory behavior of keratinocytes and fibroblasts, the important effects are those on collagen synthesis, deposition, or degradation. Among the growth factors that enhance collagen synthesis are TGF-β, IL-1, PDGF, acidic and basic FGF, and IGF. On the other hand, TNF-α, IFN-γ, and relaxin decrease collagen expression. Thus, many of the tools are now available to begin to understand the complex interactions mediated by agents that have potential therapeutic value in monolayer systems and even in three-dimensional systems in vitro.

With respect to clinical heterogeneity, diagnosis, pathogenesis, and therapy, the National Epidermolysis Bullosa Registry (NEBR) has proved to be an extremely important resource. As an orphan disease (i.e., <200,000 affected individuals in the United States and for which drug development would not be cost effective), EB displays many of the typical features: information is inadequate, diagnostic accuracy is poor, insurance coverage is insufficient, and research is only modestly or poorly funded. The NEBR has just completed its first five years of existence, during which ~1,600 patients have been entered, in large part as a result of the crucial aid given to the program by the Dystrophic Epidermolysis Bullosa Research Association of America (DEBRA). The diagnostic criteria for various types of EB have been published in guideline form [1]. The future goals of the registry are i) to continue accession of patients and longitudinal clinical characterization; ii) to provide expertise and care to patients with EB; iii) to develop a cohort of patients who can, if they wish, participate in clinical, therapeutic, and research protocols; iv) to develop novel clinical research protocols, particularly therapeutic in nature; and v) to develop banks of cells and tissues to support basic research into the pathogenesis of the various forms of EB. In this regard, it is important to note that among those individuals registered in the NEBR during the first five years, 85% were willing to consider donating tissue for research purposes and to date ~70% have done so.

MOLECULAR PATHOLOGY OF EPIDERMOLYSIS BULLOSA (EB)

Genetic linkage analyses have been recently employed to test the hypothesis that some of the BMZ macromolecules listed in Table I would serve as candidate genes in different forms of EB. This approach has been extremely fruitful towards elucidation of candidate genes in dominantly inherited families with simplex or dystrophic forms of EB. In case of EB simplex, three groups, using molecular biologic approaches, have now independently reached the conclusion that the primary defect within these families is associated with mutations in the keratin genes [2,4,5]. Specifically, some of the families have been linked to chromosome 12q adjacent to the keratin II gene cluster, whereas some families demonstrate linkage to 17q in the vicinity of keratin I gene cluster. Furthermore, discrete point mutations in keratin 14, a member of the keratin I gene family, have been detected in the simplex forms of EB [2,4]. Such substitutions in the primary sequence of keratin 14 were shown to have deleterious effects on keratin-fibril assembly both in cell-transfection experiments and in transgenic mice [2,3].

A general conclusion reached from these studies is that synthesis of a mutated keratin can have extremely severe consequences for keratin-fibril assembly through dominant negative interactions of the dimeric molecules. This information, together with recent immunofluorescence and electron microscopic demonstrations of keratin abnormalities in the simplex forms of EB, suggest that many, if not most, families with the EB simplex phenotype may be derived from mutations in keratins. However, the limited number of families studied thus far does not allow us to decide whether or not clinically different simplex phenotypes (Dowling-Meara, Weber-Cockayne, Kohnen, etc.) reflect mutations in different keratin genes. Furthermore, evidence of genetic heterogeneity within the simplex forms of EB exists. In particular, the “Ogna” variant has been linked to a locus on chromosome 8, and evidence for another mutation on the long arm of chromosome 1 has been presented [22–24]. In the latter cases, no candidate genes have been identified as yet.

In the case of dominant dystrophic EB, strong genetic linkage to the type VII collagen gene locus (COL7A1) has been demonstrated [25,26]. This progress has been made possible by identification of a PvuII polymorphism within the newly cloned human type VII collagen gene. Utilization of this polymorphic marker in COL7A1, together with other restriction fragment length polymorphism (RFLP) on chromosome 3p, has allowed us to establish linkage to type VII collagen in four families with dominant dystrophic EB. The maximum reported LOD scores (Z) vary from 2.1 to 8.8 at recombination fraction θ = 0, suggesting that the type VII collagen gene harbors the mutation causing the dominant dystrophic EB in these families [26]. In fact, preliminary evidence for a mutation in one family with dystrophic EB was shown. Elucidation of this and other mutations in the COL7A1 gene is currently in progress.

By analogy to gene mutations in other collagen genes, such as
type I collagen gene defects causing osteogenesis imperfecta, one could predict that a variety of different types of mutations could result in abnormal anchoring fibril assembly. For example, mutations in the triple-helical portion of type VII collagen could prevent or delay the secretion of this collagen from basal keratinocytes, the primary cell type responsible for anchoring fibril synthesis [27]. In support of this mechanism are recent immunofluorescence data depicting intracellular accumulation of type VII collagen epitopes within basal keratinocytes in some cases with dystrophic EB, suggesting a secretory defect [28,29]. Furthermore, mutations in the non-collagenous portion of type VII collagen, which has putative interactions with other components of the cutaneous basement membrane zone, may result in impairment of anchoring fibril function, resulting in the EB phenotype. These possibilities are currently being tested by expression of recombinant type VII collagen protein segments with mutated sequences, and development of transgenic animals, in an approach similar to the one that was employed to examine keratin mutations in the simplex forms of EB. The genetic linkage analyses have thus far identified type VII collagen as the candidate gene in the dominantly inherited cases of dystrophic EB [25,26]. In addition, ultrastructural demonstration of abnormal anchoring fibrils and the absence of type VII collagen in some cases with the recessive form of dystrophic EB suggest that type VII could also be a candidate gene in some cases with the recessively inherited form of dystrophic EB. This possibility is supported by a report excluding collagenase as the candidate gene in a family with multiple affected siblings with RDEB [30]. However, this approach was not informative in several additional families, and the possible heterogeneity within the recessive dystrophic EB remains to be elucidated by further linkage analysis.

Thus, the approaches of genetic linkage analysis have identified several candidate genes in different forms of EB, and molecular cloning of these genes has been employed to identify putative mutations both in the dominant simplex and the dominant dystrophic forms of EB. Clearly, elucidation of a large number of families with different clinical forms of EB is necessary to establish the correlation between specific mutations and the phenotypic characteristics. It should be noted that identification of these mutations provides a means to perform accurate pre- and post-natal diagnosis at the molecular level within these families. Furthermore, elucidation of the precise molecular defects allows the formulation of more rational pharmacologic approaches than has been possible in the past.

ANIMAL MODELS

A major challenge for the immediate future is to translate the new information emanating from in vitro studies to benefit the patients with EB. In this regard, the animal models of EB may be extremely helpful. Several animal models have existed in the literature, including EB simplex in canine and bovine species, recessive junctional EB in canines, and dystrophic EB in bovine and ovine (New Zealand and Swiss) species (see [31]). Three new types of animal models for EB have recently been elucidated: i) the transgenic mouse model for dominant EB simplex herpetiformis [3]; ii) a naturally occurring alpine sheep model for dystrophic EB [31]; and iii) a xenograft model for recessive dystrophic EB [32].

A disease resembling dystrophic EB exists in Swiss alpine sheep [31]. These animals experience oral, esophageal, corneal, conjunctival, and cutaneous (muzzle) blisters and erosions after trauma. Scarring results in exungulation early in life. The blisters are subepidermal in location, and the uninvolved skin displays fine, poorly formed, or absent anchoring fibrils. Using LH 7.2 anti-type VII collagen monoclonal antibody, there is no staining of the basement membrane zone of the skin, and skin extracts show no type VII collagen protein with immunoblot analysis [31].

A xenograft model for recessive dystrophic EB (RDEB) has also been described [32]. In this model, clinically unaffected skin from patients with recessive dystrophic EB is grafted onto the skin of mice with severe combined immunodeficiency (SCID). The grafted RDEB skin maintains its human specificity as assessed by antibodies to human class I antigens. Trauma-induced blistering is subepidermal with normal or absent anchoring fibrils. Neither the non-blistered or blistered skin demonstrates staining with anti-type VII collagen antibodies. Thus, this model, which maintains fidelity to the natural disease, could be employed to explore pathogenesis and to test potential therapeutic options.

RECOMMENDATIONS FOR FURTHER AREAS OF RESEARCH AND CLINICAL EMPHASIS

At the end of the conference, a panel discussion was conducted to identify critical areas of future research and clinical emphasis. The participants in the panel discussion were Eugene A. Bauer, M.D. (Stanford University) (discussion leader); R.A. Briggaman, M.D. (University of North Carolina, Chapel Hill); Isao Hashimoto, M.D. (Hirosaki University); Alan Moshell, M.D. (NIAMS, NIH); Darwin Prockop, M.D., Ph.D. (Jefferson Medical College); Ms. Sharon Wanat (Dystrophic Epidermolysis Bullosa Research Association of America); and Jouni Uttvo, M.D., Ph.D. (Jefferson Medical College).

The panel identified the following areas of research and clinical relevance to the basement membrane zone biology and epidermolysis bullosa.

Research Areas of Highest Priority

1. Identification of candidate proteins for all forms of EB through biochemical, cell biological, morphologic, immunologic, and genetic linkage approaches.
2. Continued genetic mapping and genetic linkage analysis in all forms of EB and their correlation with distinct clinical phenotypes.
3. Identification of mutations in candidate genes causing different forms of EB.
4. Identification of potential environmental factors that modify expression of mutated genes in various forms of EB.
5. Development of strategies for retrieval of fetal tissues from spontaneous and elective abortions as a means of increasing the numbers of “affected” individuals within a given kindred to facilitate genetic linkage analysis.
6. Identification of naturally occurring animal models, xenograft models, and development of transgenic mice for the various types of EB, for exploring pathogenesis and novel forms of therapy, including gene replacement therapy.
7. Development of antisense oligomer strategies to reverse or “correct” the consequences of mutated genes.
8. Aggressive development of approaches to investigate mechanisms of cancers developing in patients with severe forms of dystrophic EB.
9. Fosterage of international exchange of information and expand scientific resources to promote research in EB.
10. Organization of workshops and symposia to evaluate the state of research in EB and other heritable diseases affecting the skin and mucous membranes, at regular intervals.
11. Continued efforts to ensure the stability of research funding into the basic biology and pathophysiology of the cutaneous basement membrane zone.

Clinical Areas of Emphasis

2. Translation of molecular biologic and immunologic advances to clinical practice, especially in the realm of prenatal diagnosis and genetic counseling.
3. Long-term support for the National EB Registry as a patient care resource and as a source of cell and tissue specimens for future investigation.
4. Continued close interaction between the dermatologic investigators and clinicians with DEBRA, the major patient-advocacy organizations in the United States and several other countries.
Development of Novel Therapeutic Approaches

1. Development of innovative treatment modalities including the use of recombinant cytokines and growth factors to enhance cutaneous tissue repair and to prevent incapacitating scarring in some forms of EB.

2. Development of technologies for gene-replacement therapy in cutaneous diseases, especially through the use of keratinocyte engraftment containing transfected genes correcting the mutations.

3. Fosterage of awareness about the existence of the FDA Orphan Drug Program as a means to apply novel therapies to a small group of patients.

The panel felt confident that, with emphasis on these areas of research, the molecular basis of several different forms of EB will be delineated in the foreseeable future, and such information will be highly useful for accurate diagnosis and classification of EB. It will also form a rational basis for development of novel treatment modalities to prevent and reverse the multitude of deleterious consequences of gene mutations in this devastating group of diseases.

REFERENCES


