PSORIASIS

PROCEEDINGS OF THE SECOND INTERNATIONAL SYMPOSIUM

Edited by

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Stanford University, 1976

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Preface

In preparing the Second International Symposium on Psoriasis, queries were sent to the participants of the first symposium held in 1971 and advice and suggestions were obtained from others of varied disciplines from different countries. We were greeted with so much enthusiasm that we proceeded with active planning; and although at first doubtful that there would be sufficient new and timely work for a four-day meeting, we were encouraged by the excitement that built up during the formative stages to bring our plans to fruition.

In organizing this conference, we have been assisted by an advisory committee of the National Institute of Arthritis, Metabolism, and Digestive Diseases, which included Drs. G. Donald Whedon, Laurence Miller, Eugene Van Scott and Gerald Weinstein. Even with such excellent guidance, the conference would not have been possible were it not for the financial assistance furnished by the Westwood Pharmaceutical Company, The Stella B. Gross Trust and the National Institute of Arthritis, Metabolism, and Digestive Diseases.

The primary aim of the symposium was to examine the progress that has been made from 1971 to the present in biological and chemical research on psoriasis as well as in treatment of psoriasis. Recent information in genetic markers, the action of prostaglandins, the use of psoralens and longwave ultraviolet light as a therapeutic regimen are but a few areas that have expanded in these last five years.

These Proceedings represent 43 Plenary Papers and 55 Brief Communications that were given as poster presentations at the symposium. In the same way that they were organized for the program, the Plenary Papers are assembled here into four categories: Biological Aspects of Psoriasis, Basic Clinical Aspects of Psoriasis, Chemotherapy of Psoriasis and Photochemotherapy of Psoriasis; and the Brief Communications into the following groups: General Aspects, Cytologic Aspects, Chemical Aspects, Immunologic Aspects, Chemotherapy and Photochemotherapy.

The symposium provided an opportunity for scientists from 27 countries to think about psoriasis, to exchange ideas, to educate and to stimulate. Further

rewards from this conference will come forth when the attendees have returned to their clinics and laboratories with new information and refurbished spirit to apply to the solution of a problem that has created lifelong suffering for millions.

The editors extend their appreciation to the contributors for allowing the editorial board to change and condense papers, thereby preventing the exclusion of any presentation given at the symposium.

Valuable editorial assistance was rendered by Miss Susan Becker, Mrs. Kathryn Miles and Mrs. Sharon Maddox.

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Opening Remarks

G. DONALD WHEDON

Dr. Farber, Distinguished Participants in this Symposium, Ladies and Gentlemen:

I am very pleased to take part, as representative of one of the co-sponsoring organizations, in the opening of this Second International Symposium on Psoriasis, just five years and five days after the opening of the first such symposium in which I was also privileged to participate. At the time, I said that I saw that symposium "as a most significant and valuable part of a currently greatly intensifying effort both in this country and in many others to learn more and to do more about this serious and important disease." I think that I overstated a bit the *degree* of intensification of effort in psoriasis research and education at that time, but there is no doubt that increased efforts have been made with signs of real progress, particularly during the last two years.

Nevertheless, we have a long way to go in dealing more effectively with a disease that has such a considerable medical, personal, social and economic impact as psoriasis. Our epidemiologic data in this respect are still rather soft. We have only an *estimate* of 6 to 8 million persons with psoriasis in the United States—that is a prevalence of 3 to 4%—and prevalence ranging from 2 to 6% in a number of other populations; approximately 1 to 2% of those affected are regarded as severe cases. We have the further estimate that about 150,000 new cases occur annually. The economic burden is hard to judge except in reference to a figure from the National Program for Dermatology for all skin diseases of $1.5 billion yearly and of about $1 billion spent annually on topical preparations for the skin. I trust that new and better epidemiologic data will come out of this symposium. The most pungent statement on impact that we can make at the moment, I think, is the incalculable emotional and psychological effect on patients with severe or extensive involvement. Surely it is quite appropriate in our efforts to deal with psoriasis to couple compassion with dedicated scientific interest and effort.

On the level of effort in support of psoriasis research we have made only modest progress. In 1971 projects supported by NIAMDD specifically aimed at psoriasis amounted to less than $0.5 million, and all dermatologic research supported by the National Institutes of Health was about $15 million. At present, al-

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though the total for all dermatology has not risen very much, in relation to the *very* modest increases in National Institutes of Health funding over the past eight years, psoriasis research in NIAMDD has risen to $2 million. Despite this proportional four fold increase, the absolute amounts of funding investment toward solution of the psoriasis problem are obviously minuscule in relation to its costs, even if such costs are viewed from only the economic aspect.

Recently, however, there has been developing considerable public and Congressional interest in increasing the support for psoriasis research. Stimulated considerably, I think, by efforts of the National Psoriasis Foundation, the Senate Appropriations Subcommittee for HEW in its Report just issued on the Fiscal Year 1977 Appropriations Bill (for the year beginning October 1, 1976) has urged the National Institute of Arthritis, Metabolism, and Digestive Diseases to increase its efforts in psoriasis research and "directs the Institute to do an analysis of the needs and priorities for dermatologic research." This Senate subcommittee has voted a considerable increase in funds for 1977 for NIAMDD but the amount to become available for all of its programs including dermatology and psoriasis is uncertain because of several steps yet to be taken, *ie*, vote by the full Appropriations Committee, vote by the full Senate, compromise in House-Senate conference committee and finally the question of signature or veto by the President of the entire Labor-HEW Appropriations bill. If there is Presidential approval, completion of these several steps is anticipated by September or October.

We all agree on the need for greater research efforts in psoriasis. But just added dollars will not turn the key and unlock the door to the secret of the final perfect treatment. It is clearly just as important, if not more so, to have more good research ideas.

One of the ways of aiding this development is to train more young physicians and PhD's more effectively in the thinking and the techniques of good clinical and laboratory research. To this end the National Institutes of Health will continue to strive, through expected continuing difficulties, to make training funds and programs available for this special and important purpose.

Another way to catalyze the production of research ideas is to facilitate the exchange of information produced by research, by epidemiologic inquiry and by the experience of practice where the latter can be controlled and accurately assessed. The day of the single investigator with a sudden brainstorm is long past; it is now the time of multi-investigator and multi-laboratory research. The effectiveness of these multifaceted efforts depends on the extent to which each investigator is continually kept informed of the contributions of others. The usual publication of scientific literature in journals is the sensible system in principal use, but we should not underestimate the great importance of the meeting of investigators and clinical experts in annual professional society meetings, in workshops and in international symposia. Such personal exchanges, by both formal and informal discussions, obviously provide more rapid dissemination of results. Of equal importance, they help to assemble com-

binations of new knowledge which lead to ideas and suggestions for new directions and for selection of more promising efforts—hence, the great importance of this four-day symposium with participants from many centers and many countries.

This international symposium will fulfill, by a combination of the dynamics of the meeting itself and of publication of its proceedings, all of the functions of such meetings that we have cited. In addition, it will complement the other meetings which have been held during the five-year interval since the first symposium. I have in mind the various smaller workshops co-sponsored by our Institute and by the National Psoriasis Foundation. The most recent of these, a bit more than a year ago, developed a five-year plan which identified areas in which it was felt that fruitful research could be undertaken during the next several years. A very practical outcome of that workshop was a contract from our Institute and the National Cancer Institute for study of previously unused topical chemotherapeutic agents in therapy of psoriasis. The prime contractor is the University of Miami, Department of Dermatology, but the study will actually involve a nationwide cooperative approach.

It is customary, always, to begin a symposium of this sort with a statement of what great expectations we have for the quality and value of the information and data to be presented. These expectations are indeed valid, as suggested by various subjects on the program, such as abnormalities in blood vessels and epidermal cell growth in normal-appearing skin, abnormalities of cell-mediated immune systems, studies of the metabolism of cyclic nucleotides and their relationships to prostaglandins, mechanism of action of corticosteroids and reviews of the current status of the most effective chemotherapeutic agents. These various subjects are all indicative of the progress made over the past five years and the level of sophistication attained in the more fundamental aspects of research.

Certainly one of the most provocative and hopeful aspects in the therapeutic realm is the relatively new photochemotherapeutic combination approach of psoralens and longwave ultraviolet light. Evaluation of the data on long-term effectiveness and long-range safety accumulating in several collaborating clinics will be aided by contract support from our Institute. Although it is at least premature and undoubtedly over dramatic to compare this new treatment in psoriasis to the advent of insulin in diabetes, nevertheless similarity occurs to me in its *possible* effect on scientific inquiry in the disease. The spectacular success of insulin *anesthetized* research in diabetes for about 40 years. Let us insure that PUVA, however successful, will have rather the opposite effect and by the very nature of its obvious impact on the disease will bring about stimulation of research as well as efforts to find out just how it works and how to make it more lastingly effective, and in so doing aid in a major way in understanding the psoriasis disease process itself.

On this hopeful and expectant note of accelerating progress in both basic and clinical research and in clinical treatment of psoriasis, let us begin this important symposium.

Introduction: Unanswered Questions About Psoriasis

EUGENE M. FARBER
M. LEXIE NALL
VERA MORHENN
JAMES KAYE

The goal of most international conferences is to bring together renowned investigators from the biologic and clinical sciences to exchange views, to describe results and to discuss one another's interpretations. Thus, the Second International Symposium on Psoriasis has assembled scholars from 27 countries representing many different areas of research.

Excitement with psoriasis research is approaching a peak. Even though our problems are not solved, many new ideas are current and there is a growing and vigorous multidisciplinary thrust from laboratories and clinics in many parts of the world. A MEDLARS search of approximately 3,000 journals from 1971 to 1976 in the world literature revealed 2,867 citations on psoriasis. This represents an average of nine published papers every week on this subject over a five-year span.

At this time it is not for us to assume that there is a single road leading to the discovery of the cause and cure of psoriasis. We must remain alert to developments in every field to see how new advances might apply to psoriasis.

Even though we are in the center of a scientific exploration, there are many unanswered questions about psoriasis. We have chosen four from an array of such queries. Answers to these will require the application of many techniques derived from different scientific disciplines.

Why is There No Satisfactory Experimental Model for Psoriasis?

The unavailability of an experimental model is a serious handicap to our research. Oncologists, geneticists, virologists, microbiologists have experimental models, but we have had to carry out many of our studies with tissues that are

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difficult to procure, difficult to maintain, and which do not accurately represent the psoriatic reaction. Some approaches that have been used are:

1. *The stripping of the skin with cellophane tape.* This procedure produces hyperplasia, an increased number of mitoses, and parakeratosis, but only small areas of skin are made available for study.[1,2] Also, the initial mitotic burst is self-limited, and therefore cannot be regarded as equivalent to alterations observed in psoriasis.

2. Braun-Falco and Christophers[3] demonstrated that *repeated applications* of retinoic acid to guinea pig skin produces *psoriasiform* change in the epidermis, but the lesions cannot be maintained without continuous application of the drug. This technique, nonetheless, is of biologic interest because it simulates the lesion.

3. In 1965 Nasr and Shostak[4] fed mice a *diet deficient in essential fatty acids*. The skin developed hyperkeratotic and parakeratotic changes. However, these mice were unsuitable for any prolonged study because of illness from the diet.

4. Van Scott and Yu[5] described the use of *mouse vaginal mucosa* as a model for the screening of drugs which affect epidermal proliferation. Using this model it is possible to ascertain whether selected agents can provide sustained mitotic inhibition and if these will be of benefit after prolonged use.

5. Krueger[2,6] transplanted psoriatic skin to the *nude mouse*. This comes the closest to being a real model, but there are many problems. These animals are difficult to breed and there is a high incidence of infection.

6. Freeman[7] recently developed a *tissue culture system* which may prove to be valuable in psoriasis research. Human diploid skin epithelial cells were selectively grown on a dermal collagen bed of sterile, dead pig skin. The epithelial cultures were carried for months with up to six subdivisions on pig skin. At least 24 to 48 cell generations were produced. They formed maturing epithelium *in vitro* and upon transplantation back to the original human donor. Although this is an innovative procedure, it is still not an adequate model of psoriasis, due to the absence of a normally viable dermis. However, it may be useful to evaluate the capacity of drugs to inhibit epidermal growth.

None of these six experimental models adequately represents the psoriatic process. The ideal model would be classic psoriasis in a nonhuman primate.[8,9]

Up to now psoriasis has never been diagnosed in any animal species. When Dr. William Montagna was asked, "Why is it that nonhuman primates have nearly every disease known to man; why don't they also have psoriasis?," he replied,[10] "How do you know they don't?" Since none have been observed in captivity, Montagna said he would ask the trappers and sorters of primates for export to be on the lookout.

"It is not unlikely," he added, "that a trapper would destroy a primate ready for export, if he observed a gross disfigurement on the animal's body."

There are primate centers for biomedical research in this country and abroad.[8,11] Highest on the phylogenetic order are the anthropoid apes, with the chimpanzee being closest to man.[12]

Leukocyte Antigens	ChLA	HLA	
	Chimpanzee	Human Control	Psoriasis
		%	%
HLA = B13 (HLA13)	identified?	4	18
HLA = Bw16 (HLA16)	?	5	22
HLA = Bw17 (HLA17)	identified	8	27

Figure 1. Leukocyte antigens.

Studies have revealed that many of the leukocytic antigens present in man are also found in the chimpanzee[13] (Figure 1). This is evidence for our common ancestry. Two of the leading investigators of seroprimatology are Metzgar[14] of Duke University and Balner[15] of the Netherlands, who have identified HLA-Bw17 to be similar in the chimpanzee and human, and have preliminary data that may indicate the same for HLA-B13. Metzgar[16] has agreed to test our HLA-B13, Bw16, and Bw17 reagents in chimpanzees. Other HLA antigens associated with psoriasis are reported in this symposium from work carried out in Finland and Japan. Man, with HLA antigens B13, Bw16, and Bw17, is presumably at greater risk for psoriasis than animals having different HLA antigens. If nonhuman primates with HLA-B13, Bw16 or Bw17 were placed in a low humidity environment for an extended time and were subjected to stress and skin trauma, would psoriasis then express itself?

Even if psoriasis were to be discovered in a chimpanzee, the cost of importing and raising these animals would be great. A realistic goal is to introduce psoriasis into a lower primate. With this thought in mind, it might be helpful to examine certain diseases that occur in man that can be experimentally induced in nonhuman primates.[17]

Can a Viral Etiology of Psoriasis be Excluded?

In 1962 at the XII International Congress of Dermatology, one of us (EMF) presented a paper which speculated that a search for the etiology of psoriasis should include a search for a *"slow virus."*[18] One "slow virus" infection that has been studied extensively is kuru.[19,20] This fatal disease of the central nervous

system occurs in the Fore people in the eastern highlands of New Guinea. It is the first chronic neurological degenerative disease of man of viral etiology and the first slow virus transmitted to a laboratory animal.

At the National Institutes of Health, Gajdusek[19,20] inoculated chimpanzees intracerebrally with brain suspensions from kuru patients. The chimpanzee developed kuru after a one or two-year lapse of time. A "slow infection" of the host is caused by an agent which continues to multiply over months and years, with localization of the infectious process in a *single organ*. Psoriasis, in our opinion, is a single organ disease.

Gajdusek[19] pointed out that we should consider the possibility of an infectious etiology in many diseases that heretofore have been considered fundamentally genetic, immunologic, neoplastic or metabolic, such as multiple sclerosis, Parkinson's disease, certain types of dementia and cancer.

Slow viruses may skip a generation and produce cumulative effects of a disease, especially in inbred populations.[9] The "slow virus" hypothesis might well be tested in the inbred population of the Faroe Islands where there is 91% occurrence of familial psoriasis.

In searching for a viral etiology, we are fortunate that modern virology now offers the technology to answer questions such as whether a slow virus or some other viral agent is operative in a specific disease.

Examples of the techniques that might be employed to establish a viral etiology for psoriasis are:

1. *Electron Microscopy*—Until now, no virus has been recognized,[21] but this technique may still offer some promise.
2. *Tissue Culture*—Homogenates from psoriatic plaques have been added to eukaryotic cells *in vitro*,[1] but no evidence for the effects of a virus has been observed.
3. *Viral Liberation*—If a virus is integrated into the cellular genome of psoriatic cells, as has been suggested recently by Lennette for certain animal tumors,[22] treatment of psoriatic plaques *in vitro* with known viral liberating agents, such as iododeoxyuridine or UVB, might release virus particles.
4. *Infection*—In order to show that a disease-associated virus represents the etiologic agent, one must be able to prove that inoculation with the virus results in expression of the disease.

Even if a virus was found to be associated with psoriatic tissue, and isolated, ethical considerations would not permit the injection of a putative psoriasis virus into humans. Therefore, we must attempt to establish a nonhuman host for psoriasis. This should have a high priority, for if an animal model is developed, many experiments which are not permissible at present could be performed.

Will Seroepidemiology Help in the Elucidation of the Etiology of Psoriasis?

In the past, traditional epidemiologic techniques have been used to collect data on the natural history of psoriasis. Family and twin studies, sibships and

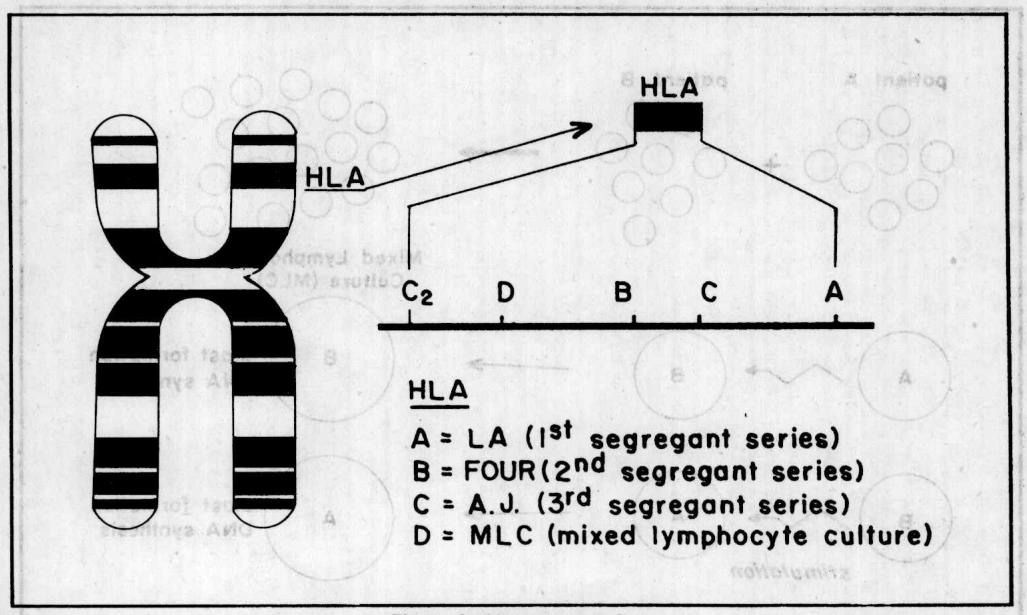

Figure 2. Chromosome 6.

pedigree analyses, provide insight into modes of inheritance. The Stanford studies indicate that the best model for psoriasis is that of multifactorial inheritance.[23-25] This implies that multiple genetic factors and environmental stresses are necessary for the manifestation of disease.

There is strong evidence that some of the genetic factors predisposing to psoriasis are either included in the major histocompatibility (HLA) locus (Figure 2) or are linked closely enough to the HLA region that certain HLA genes are markers for disease susceptibility in a large number of patients.[26-29] The HLA region of human chromosome 6 determines several cell-surface antigens which play a role in host immune functions. Burnet has hypothesized that the major histocompatability locus might serve to protect the mother against invasion of fetal tissues during pregnancy.[30] We now know that organ transplantation is most successful when donor and recipient are HLA-matched siblings.[31]

We have recently been investigating one site in the HLA locus (HLA-D) to determine its possible association with susceptibility to psoriasis. HLA-D gene products are among the antigens on the surface of lymphocytes. They determine reactivity in the mixed lymphocyte reaction.[32] In the mixed lymphocyte reaction (Figure 3), lymphocytes from patients A and B, two antigenically different individuals, are cultured together for four to six days. At the end of this time, one can observe the transformation of lymphocytes into blast forms or one can demonstrate that there has been a burst of DNA synthesis in response to the "foreign" lymphocytes. To determine which of two lymphocyte populations is responding, the one-way mixed lymphocyte reaction is used (Figure 4). Here,

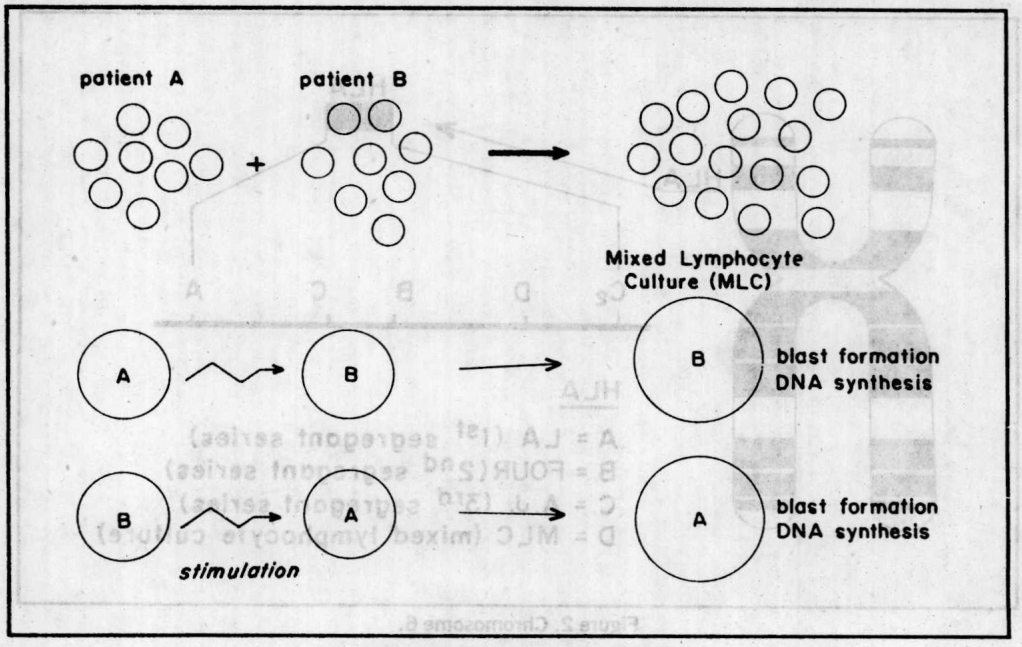

Figure 3. Mixed lymphocyte reaction.

lymphocytes from one patient (A) are irradiated before they are cultured, and therefore no longer can synthesize DNA; these cells are called "stimulators". Only the nonirradiated population of lymphocytes from patient B then responds with a burst of DNA synthesis and blast formation.

In collaboration with McDevitt's laboratory at Stanford, we have recently used the one-way mixed lymphocyte reaction to show that there is a 30% association between lymphocyte-determinant 17 (LD17) at the HLA-D locus and psoriasis susceptibility in a population of 40 psoriatics.[33] Dermatitis herpetiformis,[34] multiple sclerosis,[35] and myasthenia gravis[36] are several other diseases in which an increased frequency of certain HLA-D types is found among affected individuals.

There are several popular hypotheses concerning the association of HLA types and disease. One idea is that HLA genes are simply markers for genes which are closely linked and which actually produce disease susceptibility. Another hypothesis is that the HLA gene products are directly involved in the etiology of the disease. These cell-surface antigens could be receptors for virus, and might be a prerequisite for infection. On the other hand, these antigens may become altered upon infection in such a way as to alert the host immune system that infection has occurred. Finally, they might themselves cause the disease through interaction with molecules in the membranes of other cells.

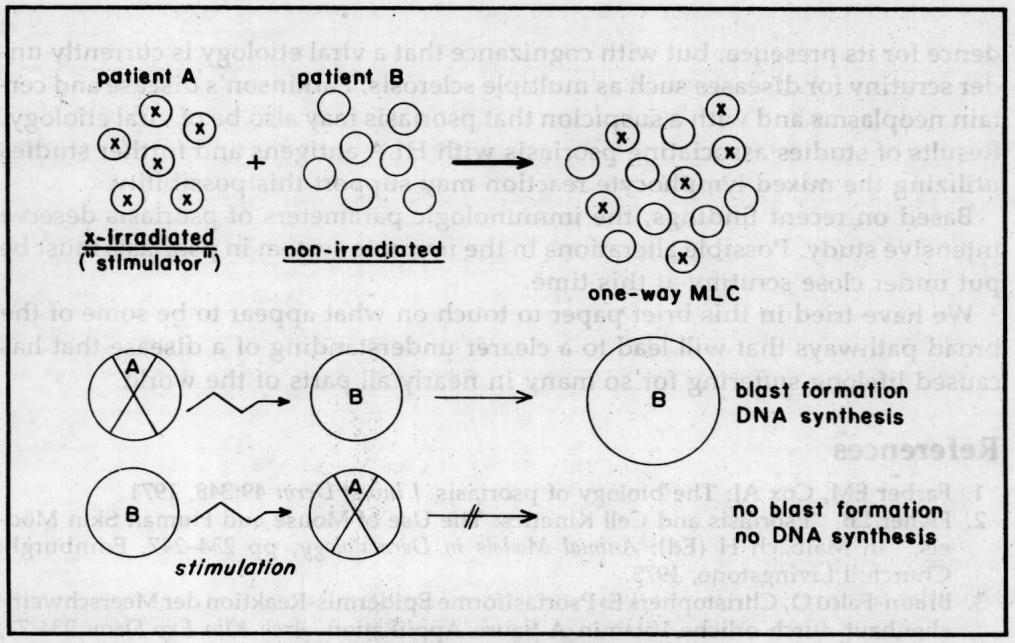

Figure 4. One-way mixed lymphocyte reaction.

Is There a Psoriasis-Specific Antigen Which will Provide a Better Understanding of the Etiology of Psoriasis?

There is no answer to this question except the reiteration that there is a similarity between our present knowledge concerning the immune system in psoriasis and that which prevailed in tumor immunology prior to the concepts of blocking antibody and immune surveillance.

The basis for the recent and rapid development of tumor immunology was the demonstration of tumor cell–specific surface antigens. A direct search for a psoriasis-specific antigen could be fruitful; many reports concerning the search appear in this symposium.

There are subtle signs that psoriatic patients show somewhat suppressed cellular immunity while they may be hyperproducers of antibody.

Summary

We have stressed the importance of developing a readily available experimental model for *in vivo* studies of psoriasis, and the importance of developing *in vitro* models more representative of the psoriatic process than those currently available. Development of one or both would accelerate our research and make many more projects feasible.

We have speculated about a viral etiology of psoriasis without any hard evi-

dence for its presence, but with cognizance that a viral etiology is currently under scrutiny for diseases such as multiple sclerosis, Parkinson's disease and certain neoplasms and with a suspicion that psoriasis may also be of viral etiology. Results of studies associating psoriasis with HLA antigens and further studies utilizing the mixed lymphocyte reaction may support this possibility.

Based on recent findings, the immunologic parameters of psoriasis deserve intensive study. Possible alterations in the immune system in psoriasis must be put under close scrutiny at this time.

We have tried in this brief paper to touch on what appear to be some of the broad pathways that will lead to a clearer understanding of a disease that has caused lifelong suffering for so many in nearly all parts of the world.

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