How a Cancer Trial Ended in Betrayal

Part I—"Background"

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Birmingham, Alabama— After Bob Lange spent 8 weeks rubbing an experimental cream, BCX-34, from a prominent biotech company BioCryst, on the fiery patches on his body, researchers at the University of Alabama at Birmingham told him the drug was defeating the killer inside him. He felt grateful. "I believed it," he recalls. "I actually thought I might be cured."

But it was a lie. The drug had no effect on Lange's rare and potentially fatal skin cancer. And the two key people testing the drug knew it. Lange and 21 other patients were victims of fraud—a scheme made possible by the close tie between the university and the state's most prominent biotech company.

—*The Baltimore Sun*, June 24, 2001

In this case study, we will conduct a small-scale "clinical trial" in class to simulate the above real clinical trial that was conducted by the University of Alabama at Birmingham and the biotech company BioCryst to study the effects of an experimental drug, BCX-34, in treating skin cancer (malignant) cutaneous T-cell lymphoma. The objectives of this case study include the following:

- to learn the basics of scientific research in a clinical trial;
- to learn the principles of the scientific method; and
- to consider the ethical issues involved in clinical trials.

Please write concise answers to the following questions:

1. What was the disease being treated?
2. What was the drug being tested?
3. What was the *hypothesis* underlying the clinical trial?
4. What kind of *experiments* could be used to test the hypothesis?

Image Credit: Detail from "Job and His Wife" by Albrecht Dürer, c. 1504.
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Part II—"The Main Characters"

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The following are the main characters involved in the clinical trial that was conducted by the University of Alabama at Birmingham and the biotech company BioCryst. Please pay special attention to the job descriptions for the clinician and the scientist. You will be asked to play these roles in a simulated clinical trial.

- **Bob Lange and 21 other patients**, who had a rare and potentially fatal form of skin cancer, were participating in the clinical trial of BCX-34 directed by Dr. W. Mitchell Sams Jr., Chairman of the Department of Dermatology at the University of Birmingham at Alabama.

- **Harry W. Snyder Jr.—MD**
  Dr. Snyder was the scientist who ran the BCX-34 studies for BioCryst. Job description for the scientist:
  - Prepare the experimental drug for clinical use. Half of the tubes should contain the experimental drug and half should contain the placebo.
  - Generate random codes for the tubes. Keep a record (the KEY) on the code of the tube and whether it contains the experimental drug or a placebo. This KEY is confidential and should only be seen by the scientist during the clinical trial.
  - At the end of clinic trial, obtain the Clinical Record from the clinician and compare it with the KEY to correlate the treatment effect and the presence or absence of the experimental drug in the treatment.

- **Renee Peugeot—RN**
  Ms. Peugeot, a nurse, was given "total responsibility" by Dr. Sams to conduct the company-funded study of BCX-34 in clinics. Job description for the clinician:
  - Distribute coded tubes of cream to patients to rub on their skin lesions. Keep a record of the code on the tube and to which patient the tube is distributed. The codes on the tubes are randomized and do not contain information on whether a particular tube contains the experimental drug or a placebo.
  - Monitor the size of skin lesions by tracing the circumference. Record changes in the size and colors of the lesion during the treatment.
  - Keep a Clinical Record of the treatment effect on the patient. This Clinical Record is confidential and should only be seen by the clinician during the clinic trial.

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Part III—"Clinical Trial"

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The class will be separated into two groups. One group will play the role of the clinician (the Clinician Group), and the other group will play the role of scientist (the Scientist Group). One person from each group will be asked to play the role of Peugeot (a clinician) and Snyder (a scientist), respectively. This sub-group will be referred to as the "Peugeot-Snyder" group. The people in this sub-group will receive special instructions provided by the instructor.

Scientist Group Exercise

1. Assign codes (for example, using three-digit numbers: 867, 705, etc.) to 10 index cards that represent tubes of cream in the clinical trial.
2. Randomly pick 5 cards to contain the experimental drug and 5 cards to contain the placebo. Keep a record (the KEY for the clinical trial) of the code on each card and whether it contains the experimental drug or placebo. ***Keep the KEY confidential during the clinical trial.***
3. Give the coded cards to the Clinician Group.

Wait for the Clinician Group to hand over the Clinical Record. In the meantime, read about the Clinician Group exercise.

Clinician Group Exercise

Wait for the coded cards from the Scientist Group. In the meantime, read about the Scientist Group exercise.

1. After receiving the coded index cards from the Scientist Group, give one card to each "patient," who is represented by one sheet of paper that contains two photos of skin lesion (see Handout).
2. Monitor the size of skin lesions in the photo by tracing the circumference. Compare the lesion size *before* and *after* the treatment. Record the effect of treatment on each patient. ***Keep the Clinical Record confidential during the clinical trial.***

After the Scientist Group and the Clinician Group have completed the above tasks, the two groups convene to open the KEY and to correlate the treatment effects with the presence or absence of the experimental drug in the treatment.

Compare the results obtained by the large group (Scientist Group and the Clinician Group) with that obtained by the "Peugeot-Snyder" group. Discuss any discrepancies that might exist between the two.

CASE TEACHING NOTES for "How a Cancer Trial Ended in Betrayal"

by
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INTRODUCTION / BACKGROUND

Case Summary: After reading a newspaper story which documents a fraudulently conducted clinical trial involving a treatment for cutaneous T-cell lymphoma, students simulate their own small-scale "clinical trial" in the classroom. The simulation involves a secret breaching of a blind test and manipulation of data to favor a positive BCX-34 effect in treating the cancer. In one step of the trial simulation, students are presented with photographs of skin lesions from patients. Each patient has a "before" and "after" photo showing the effects of topical application of BCX-34. To determine progress, students measure the relative sizes of the skin lesions by tracing the circumferences.

Background: This case study provides students with an opportunity to learn about the complexities and issues associated with clinical trials, particularly studies that may involve the treatment of very serious medical conditions. A clinical trial is a scientific investigation of a drug's effects on humans. It is the final step in the development of a new drug, following the study of the drug's pharmacological and toxic effects on laboratory animals. This case study presents a comprehensive tool for teaching students about both the scientific methods and the ethical issues involved in clinical trials.

The case is based on a real clinical trial conducted by the University of Alabama at Birmingham and the biotech firm, BioCryst, to study the effects of an experimental drug, BCX-34, in treating skin cancer (malignant) cutaneous T-cell lymphoma. To give students a taste of the scientific research process, the case includes a simulation of the clinical trial so that students can personally experience a small-scale research project. This classroom exercise can be fine-tuned to emphasize various aspects of a clinical trial.

Developed for first- or second-year college students, the case focuses on the scientific method, with special attention to the issues of objectivity and ethics in scientific research. As such, it would be a good case for an introductory science course for science majors or for a non-majors science course. The material in the case study can be adapted to emphasize other topics, such as the pathophysiology and treatment of cancer. The case can also be tailored to specific student populations. For example, health professional students could be provided with more information on the drug approval process (pre-clinical and clinical trials), T-cell lymphoma, and the effects of BCX-34.

Objectives

- To demonstrate the basics of drug testing in a clinical trial.
  The simulated clinical trial is designed so that students gain first-hand experience in conducting a scientific research project in a classroom setting.

- To teach the principles of the scientific method.
  By guiding students through the research project step-by-step, one can teach them about the principles of the scientific method used along the way.

- To discuss the ethical issues involved in clinical trials.
  The fraud committed in the real clinical trial for BCX-34 demonstrates a typical example of unethical conduct in scientific research. This case provides an excellent opportunity to discuss factors that may influence the quality of scientific research.

CLASSROOM MANAGEMENT

This case study can be used in classes of various sizes. A basic unit for conducting the simulated clinical trial, described in detail below, includes 10 students in the Scientist Group, 10 in the Clinician Group, one student playing the role of Snyder, and one playing the role of Peugeot. If the class is smaller, students would need to see more "patients"; if the class is larger, duplicate sets of handout could be used for two or more clinical trial units.

To help prepare the students for the case study, briefly provide them with some background information in the form of a mini-lecture or a separate handout on cutaneous T-cell lymphoma and BCX-34:

- *Cutaneous T-cell lymphoma* is a disease in which T-cells of the lymph system become cancerous and affect the skin. Cutaneous T-cell lymphoma usually develops slowly over many years. In the early stages of the disease, the skin may become itchy and dry, and dark patches may develop on the skin. As the disease progresses, tumors may form on the skin, a condition called mycosis fungoides. As more of the skin becomes involved, the skin may become infected. The disease can spread to lymph nodes or to other organs in the body, such as the spleen, lungs, or liver.

- *BCX-34,* or 9-(3-Pyridinylmethyl)-7H-9-deazaguanine, acts by inhibiting purine nucleoside phosphorylase, thereby preventing the activation of T-cells [for more information, see Bantia et al. 1996]. BCX-34 also inhibits the replication of infected T-cells.

Give the students Part I of the case, which presents a brief newspaper story about a clinical trial that was conducted to test the effects of the experimental drug BCX-34 on cutaneous T-cell lymphoma. Ask the students to read the newspaper account of the clinical trial and answer the questions that follow. In class, discuss the hypothesis of the clinical trail based on the background knowledge they were provided on cutaneous T-cell lymphoma and BCX-34.

Next, give students Part II, which provides more details of the clinical trial. Discuss in class the experimental design phase of a human clinical trial.

Then give students Part III, which contains the materials for the simulated clinical trail. Separate the class into two groups. One group plays the role of the *clinician*; the other, the role of the *scientist*. Give the Scientist Group 10 index cards that represent the tubes of cream in the clinical trial. Give the Clinician Group the 10 sheets of skin lesion photos. Each sheet represents one "patient" and contains

two images of a skin lesion, before and after treatment. Each image pair is based on a single photo whose size has, in some cases, been diminished or cropped to illustrate "progress." The sheets are intended to serve merely as examples of how the case might be presented. Because of copyright restrictions we could not include more images in the case, but anyone interested in researching additional images to include in their classroom can turn to the sites listed in the references.

Ask one volunteer from each group to play the roles of Peugeot (a clinician) and Snyder (a scientist). These students each receive a duplicate set of the index cards and skin lesion photos and are directed by the instructor in private that they are to breach the blind test and manipulate the data to favor a positive BCX-34 effect in treating the cancer.

Below are the instructions for the two groups.

Scientist Group Exercise

1. Assign codes (for example, using three digit numbers: 867, 705, etc.) to 10 index cards. During the classroom simulation, these index cards represent tubes of cream that will be given to the patients. The number of cards may vary with the number of students. Please note that since the number of cards needs to be limited to a manageable size in this exercise, the sample size may not be large enough for obtaining statistically significant results. However, this does not affect the goal of this exercise, which is to experience scientific research in action.

2. Randomly pick 5 cards to represent the experimental drug and 5 cards to represent placebo. Keep a record of the codes and whether they represent the drug or not (the **KEY**, or Randomization Schedule). **Keep the KEY confidential during the clinical trial.**

3. Give the coded index cards to the Clinician Group. Wait for the Clinician Group to hand over the Clinical Record. In the mean time, read about the *Clinician Group Exercise*.

Clinician Group Exercise

1. While waiting for the coded index cards from the Scientist Group, read about the Scientist Group Exercise.

2. After receiving the coded index cards (tubes of cream) from the Scientist Group, give one card to each "patient." Each patient is represented by one sheet of skin lesion photos.

3. Monitor the size of skin lesions in the photo by tracing the circumference. Each patient has two photos of skin lesion, showing the lesion *before* and *after* the treatment.

4. Record the effect of treatment on each patient. Keep the Clinical Record confidential during the treatment.

5. At the end of clinical trial, present the Clinical Record to the Scientist Group.

Have the two groups get together to analyze data and discuss the results from the simulated clinical trial. Then, ask the two students playing the parts of Snyder and Peugeot to present their results. In class, discuss the discrepancies that might exist between the two sets of results.

To wrap-up, summarize the stages of scientific investigation:

1. proposal of hypotheses based on previous knowledge;
2. design of experiments to test the hypotheses;
3. experimentation, data analysis, and summarization of results;
4. communication of results to other people; and
5. evaluation of evidence and determination of whether the previous hypotheses need to be modified, followed by development of further hypotheses.

The following are suggested follow-on questions:

1. *Does the method used to determine lesion size provide an objective measurement?*

   Because there is no clear boundary between a lesion and the surrounding normal tissue, determining the circumference of lesions depends largely upon a given clinician's judgment.

2. *What method was used to minimize the subjectivity that might be involved in the experiments?*

   Discuss in detail the "double-blind test" technique commonly used in clinical settings. Emphasize the need for objectivity in scientific research.

Students will naturally be interested in what actually happened in the clinical trial conducted by BioCryst and the University of Alabama at Birmingham. Peugeot and Snyder were married to one another and owned stocks of BioCryst. A double-blind test was not carried out. Snyder told Peugeot which tube contained the drug. Peugeot forged the data utilizing the ambiguity in measuring the lesion size. Snyder also modified the data to favor a positive drug effect. The couple manipulated the clinical trial to gain approval of the experimental drug in order to increase the value of their stock in the company. Eventually, Peugeot and Snyder were convicted of defrauding the U.S. Food and Drug Administration (FDA). Dr. Sams, under whose direction the clinical trial was conducted, was banned from testing drugs for the FDA and eventually retired from the University of Alabama at Birmingham. In addition, the National Institutes of Health accused the university of poor oversight and suspended enrollment of patients in 550 studies. Investors in BioCryst lost an estimated $34 million after the bogus data were discovered.

Points to ponder:

1. Is it possible to eliminate subjectivity in scientific research? What methods can be used to reduce subjectivity?
2. What are the dangers in mixing commercial interests with scientific research? How might the dangers be minimized?

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- Busted! Couple Imprisoned for Faking Data (*ScienceNow*) http://bric.postech.ac.kr/science/97now/00_9now/000908c.html
- Cutaneous T-Cell Lymphoma, Mycosis Fungoides, and Sezary Syndrome (*Lymphoma Information Network*) http://www.lymphomainfo.net/nhl/types/ctcl-mf.html
- Dermatology Image Atlas (*Johns Hopkins University*) http://dermatlas.med.jhmi.edu/derm/
- FDA Drug Approval Process (*Food and Drug Administration)* http://www.fda.gov/cder/handbook/develop.htm
- Good Clinical Practices in FDA-regulated Clinical Trials (*Food and Drug Administration)* http://www.fda.gov/cder/guidance/959fnl.pdf

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Image Credit: Detail from "Job and His Wife" by Albrecht Dürer, c. 1504.
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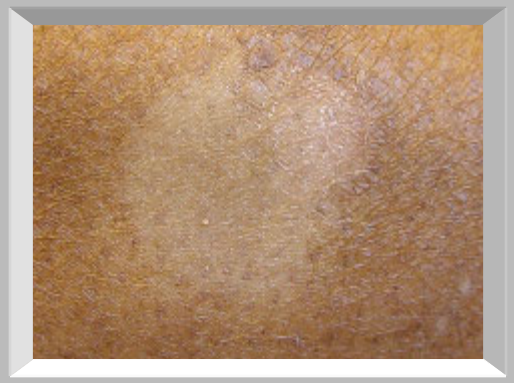

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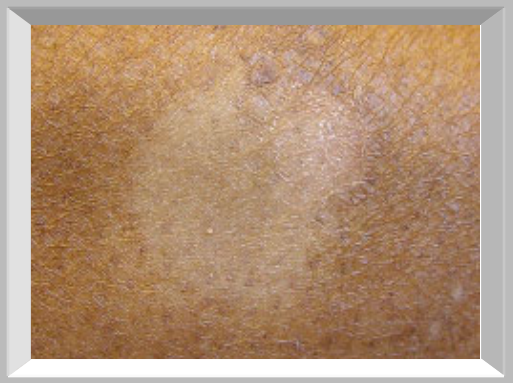

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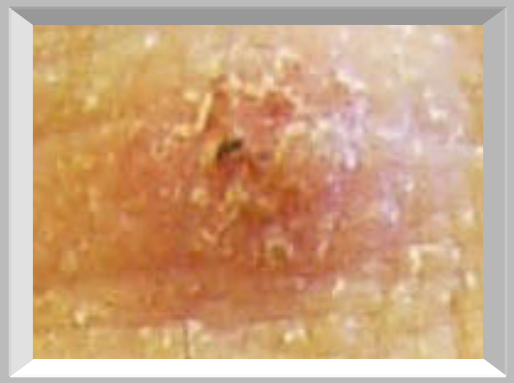

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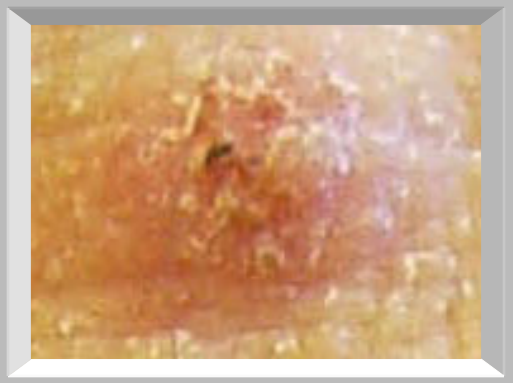

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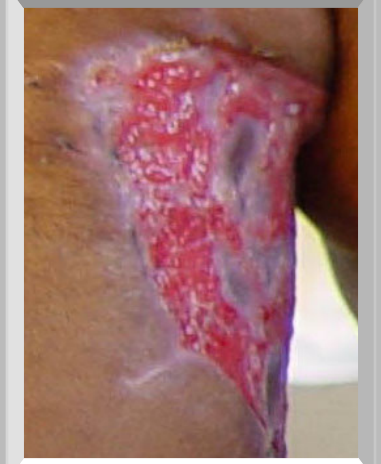

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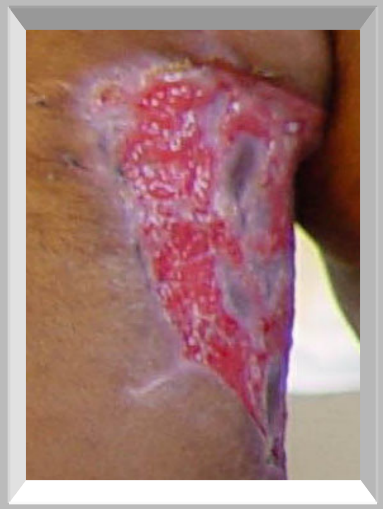

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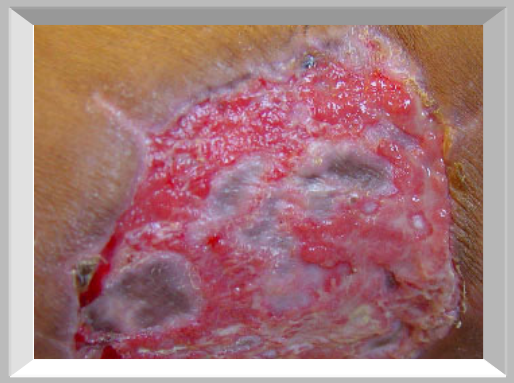

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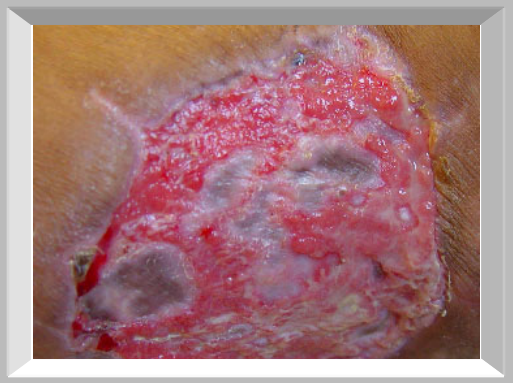

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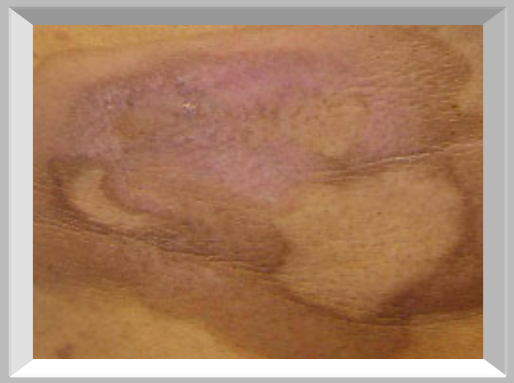

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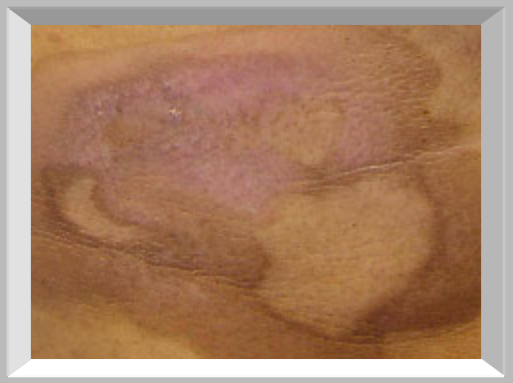

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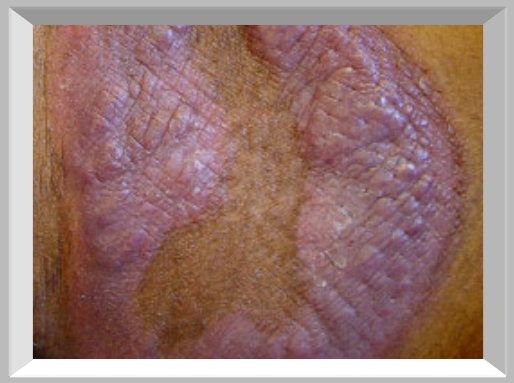	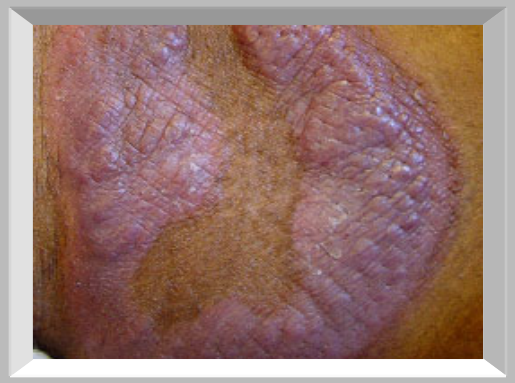

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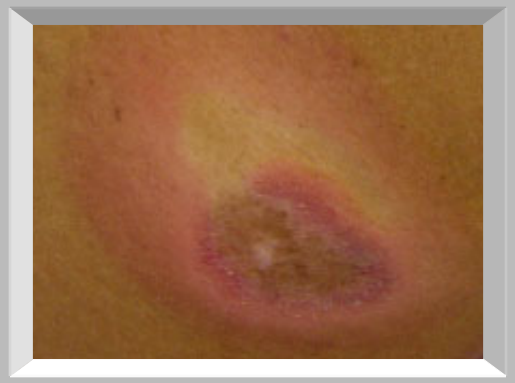

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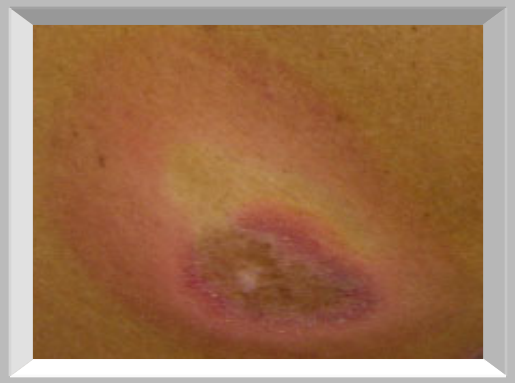

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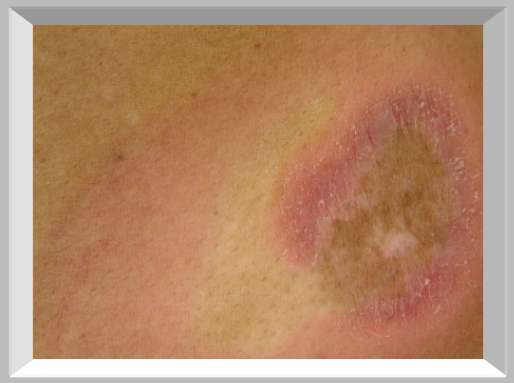

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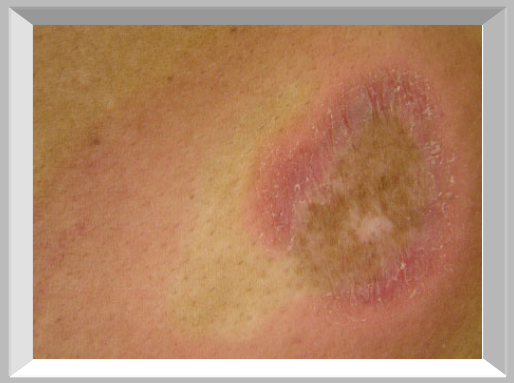

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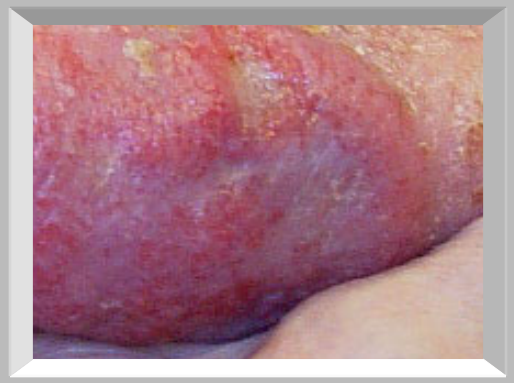

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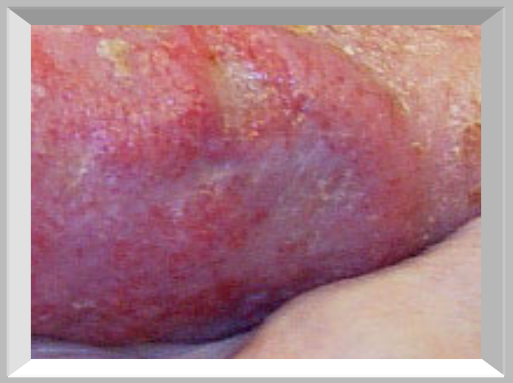

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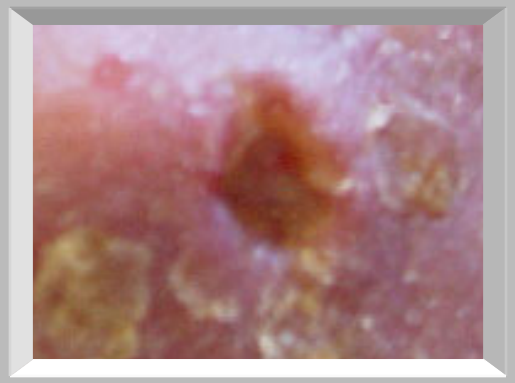

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