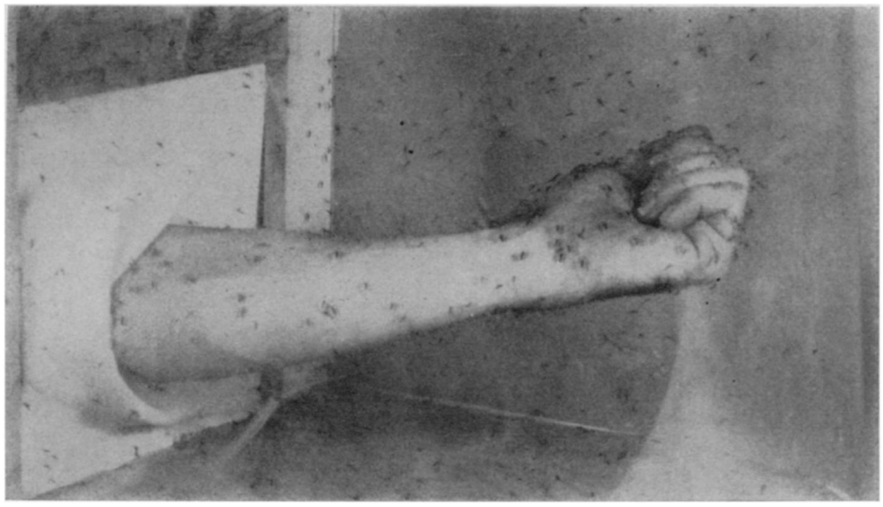


WHO

In the search for drugs, a volunteer invites malaria from infected mosquitoes.

CLINICAL TESTING

Consent: It's the Law

Informed consent for human testing, investigators say, simply frightens patients and irritates doctors.

by Barbara J. Culliton

American soldiers in Vietnam can be cured of malaria because prisoners in Atlanta offered their arms to mosquitoes and experimenters' needles in the search for antimalarial drugs.

German measles is on the way out because 34 children in Arkansas were inoculated with untried vaccines.

Every modern surgical technique had to be tested for the first time on some human guinea pig.

And, as pharmacologists become more sophisticated about studying drug behavior, the more convinced they are that what proves safe in animals will not necessarily be safe in humans. Thalidomide, for example, has no effect on rat embryos, but causes hideous limb deformities in unborn children. Drugs must be tested on humans.

The very notion of medical testing conjures up in many minds an image of helpless victims ruthlessly exploited in the name of science. Last winter, New York State Senator Seymour R. Thaler painted details into that image when he charged officials with abusing poverty-stricken patients in New York hospitals.

Doctors promptly denied amputating deformed limbs just for purposes of surgical demonstration and said no alcoholics had died as a result of tests on their livers. But the controversy is still unresolved.

Ever since Hippocrates wrote the oath by which doctors pledge to heal, physicians have been trying new drugs and treatments on humans, searching for ways to prevent and cure disease. For this, the clinical investigator would like to be a hero; instead, he finds, the public often sees him as a villain.

Defensively, he says he is neither a Nazi nor a lunatic, and that which is good for science will also be good for the persons on whom he experiments. And, he adds, most U.S. hospitals have elaborate rules for approving and conducting human tests.

But these codes are new. "In the 1940s and 50s," one cancer researcher says, "there was no such thing as informed or written consent. We just carried out our tests and no one bothered much about it."

In the 1960s, however, Senate investigators with Senator Kefauver's subcommittee began turning up cases of patient abuse and incidents in which patients participated in experimental studies without knowing it. The drug industry was bringing out hundreds of new drugs every year—drugs that physicians were testing on their patients. The Senate, to minimize irresponsible use of experimental drugs and to protect prospective subjects from investigators' enthusiasm wrote this protection into law.

And a year ago next month the U.S. Food and Drug Administration ruled that doctors could no longer test any drugs on humans without first getting their patients' informed consent—in writing.

When FDA spelled it out in black and white, the regulation created quite a furor. And despite modifications, the furor is still going on. Investigators balk at what they see as a bureaucratic restriction that does little to safeguard the patient and much to undermine that patient's trust in the doctor's competency and judgment. To obtain written consent for every test, even those involving virtually no risk with drugs that had already been extensively studied, seems ludicrous and downright impossible to many investigators. They resent the implication that they are untrustworthy. Further, they say, the requirement that patients be informed of every conceivable side effect and then agree in writing to what is probably no risk at all threatens to scare people away from clinical research and make the investigators' job difficult, if not impossible.

Things became so heated at one point that Dr. Irvine Page, then research director of the Cleveland Clinic, halted all clinical testing. Other institutions threatened similar action, and physicians had visions of this country's 6,000 clinical investigators out on strike to spite the FDA.

But tempers cooled, patients did not retreat by the thousands to the safety of old remedies, the FDA modified its stand and research went on.

Under pressure, FDA had agreed to require written consent only during the first two phases of drug testing. When large-scale, phase three testing begins, FDA agrees, oral consent is enough.

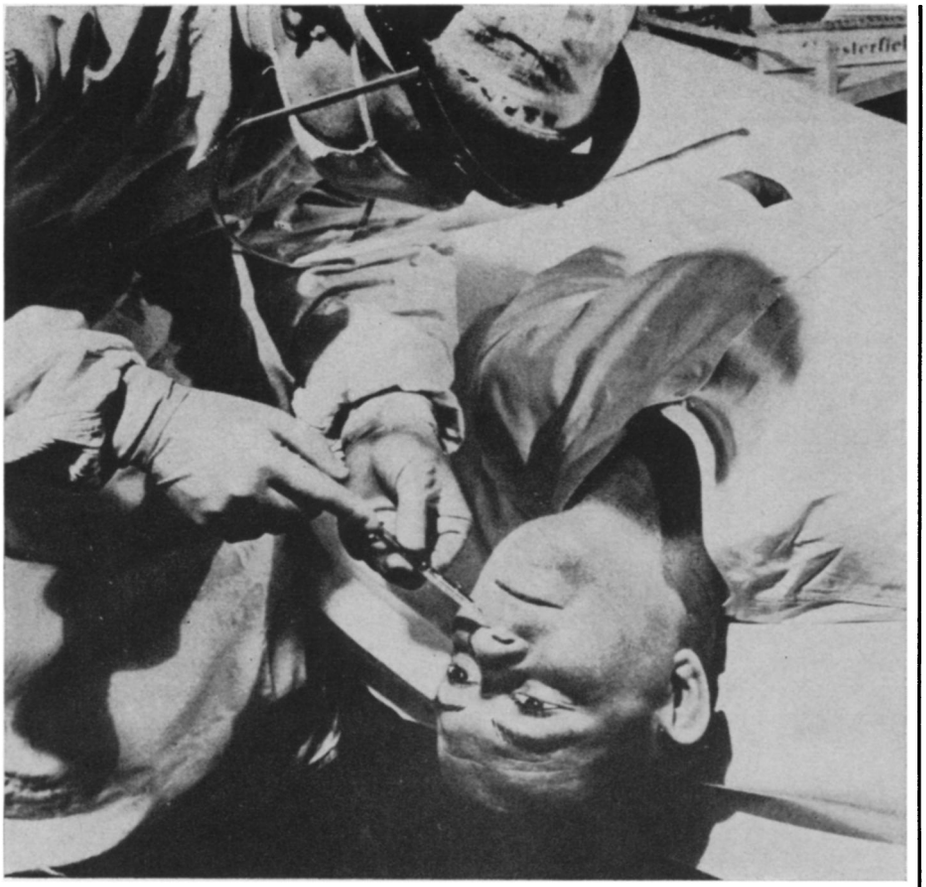
According to FDA regulations, phase one testing involves healthy volunteers —often prisoners, medical students, sometimes the investigators themselves. It can be carried out only by researchers who can demonstrate special knowledge of human pharmacology.

If, in phase one testing nothing goes wrong, phase two studies—on diseased patients—begin. Presumably, at this point there is reasonable evidence that the drug is safe. Next in line is proof of its effectiveness.

Patients must be carefully selected by physician-investigators who are familiar with the disease under study. The physician, whose guideline should be "Primum Non Nocere"—First Do No Harm—must be convinced that his patient has more to gain than lose, says Dr. Thomas C. Chalmers of Tufts University Medical School.

In both cases, written consent is required by law. Its purpose is to guarantee that the patient is not unwittingly subjected to medical experimentation and to spare the investigator from possible accusations later on.

In fact, investigators generally agree, written consent does neither of these



Human guinea pigs submit to infections so doctors can try new cures.

things, in spite of FDA's good intentions.

Dr. Richard Landau of the University of Chicago suggests investigators are more responsible, more careful, when they bear full responsibility for their research. Dr. Chauncey Leake of the University of California Medical Center, San Francisco, says written consent "may operate to reduce the care and caution which doctors and hospital staff must always exercise in regard to any patient, whether undergoing treatment, diagnostic procedures or direct experimentation."

And, even when airtight consent forms have been signed in accordance with regulations, patients or volunteers can still file suit for alleged damages. Legally, a consent form in and of itself does not necessarily have any value at all, says Charles Gozonasky of the legal department of the National Institutes of Heatlh, Bethesda, Md.

"I would like to get the law out of medicine," says Dr. Nathaniel Berlin of NIH. He finds no real problems in obtaining consent from NIH patients, but says the forms often make patients apprehensive. "Problems of consent arise only when something goes wrong —most likely in surgical cases," he says. But even this is rare at NIH.

"The important thing in human testing is to know what you're doing," Dr. Berlin says. FDA rules do little to help this. "The situations that are unacceptable to FDA are also unacceptable to any board of competent researchers," he says.

Except for concern about the nature of the doctor-patient relationship in medical testing, the patient is often neglected in discussions about consent and ethics and the law. But the fact remains that experiments with drugs or new procedures inevitably represent a risk to the volunteer, and in even the most carefully designed and conscientiously executed of experiments, it is possible that something may go wrong.

One solution, suggested by Dr. Chalmers and others, concerned about physicians' liability and compensation to the patients, is to inaugurate an insurance plan to cover patients and volunteers. Policies could be taken out commensurate with the risk involved. This plan, many investigators agree, would go a long way toward compensating unlucky subjects and would also encourage an added measure of care on the part of investigators and their institutions, which would pay the premiums.