the stated reason for establishment of a military base on Aldabra—that England needs a point where Far East-bound planes can take on food and fuel.

There are, they point out, two other routes already open. One of these is via Cyprus, Bahrain and the island of Gan in the Indian Ocean. The other, longer but less involved politically, is across the U.S. and the Pacific Ocean.

Barring war with the United States or military intervention in Southeast Africa, the critics acidly observe, there is no need for a base on Aldabra or anywhere near it—unless, they hint, there is more to America's willingness to pay half the cost than has been publicly stated.

Healey, after negotiations with a Royal Society delegation on May 22, promised that a decision on whether or not to go ahead with the base would be forthcoming within a year.

Whether this will now be shortened to produce a decision this fall as a result of the Royal Society expedition is not yet known. But if the base is ever built it will be over the massed dead bodies of most of the British and American scientific community. ◈

PHARMACOGENETICS

Heredity and drug reactions

Penicillin cures most of the thousands of patients who take it every year but it also kills hundreds of others whose tolerance for the antibiotic is zero.

Aspirin relieves some persons' headaches and makes others sick.

Sleeping pills that give some individuals eight hours sleep wear off in others in four or five hours.

Man's reactions to drugs are as personal and varied as his fingerprints and this same individuality of response also applies to the millions of animals scientists use in initial experiments on new drugs.

For three days last week eminent researchers meeting at the New York Academy of Sciences' first international symposium on pharmacogenetics reported on the complex hereditary and environmental influences that determine drug behavior in man and animals. The staggering thrust of what they said is that genetic make-up plays a definite but as yet undefined role in a person's reaction to a particular drug, that environmental factors including temperature, time of day and other drugs a man may be taking all have their effects and that the old truths about some animal species being categorically better experimental models than others may not be true at all.

In studies of an antituberculosis drug, for instance, Dr. David Price Evans of the University of Liverpool learned that Caucasians generally are slow to react whereas Eskimos and Japanese respond rapidly.

Speaking of disturbing differences in drug response between animals and humans, Dr. Kurt Hirschhorn of Mt. Sinai School of Medicine in New York pointed out that thalidomide, the tranquilizer that deforms unborn children, generally has no ill effects on rat fetuses. Aspirin, on the other hand, is lethal to unborn rats. By that logic, thalidomide would be on the market today and aspirin would not; it was because of this difference in response that thalidomide was not spotted as a teratogenic agent until it deformed hundreds of European children. The answer to such problems, according to Dr. Hirschhorn, is somehow to do studies in man.

Because pharmacologists are becoming more and more sophisticated and their understanding of drug behavior more and more precise, the future of medicine is very bright indeed. Nevertheless, pharmacology is still in its infancy and, for the present, the rapid advances scientists are making merely promise to make drug studies more complicated than they already are.

During the last couple years, a number of scientists across the country, studying the way mice metabolize hexobarbital and other common barbiturates, have reported varying results. At the Academy meeting Dr. Elliot Vesell of the National Institutes of Health, Bethesda, Md., offered a partial explanation for this. "Mice who sleep on maple shavings sleep better than mice who sleep on red cedar bedding," he said. About a year ago Dr. Vesell, who has been investigating hexobarbital metabolism, observed a dramatic shortening in drug-induced sleeping time in his experimental animals; the change occurred when bedding in cages was changed from hardwood shavings to soft—red cedar, white pine or ponderosa pine. Bedding had been changed simply because laboratory odors improve considerably when animals are kept on aromatic softwood beddings.

Following up the dramatically altered drug response, Dr. Vesell discovered that something in the softwood—probably a terpene substance—directly affects enzyme activity in the mouse livers. This substance, he reports, increases the amount of hexobarbital oxidase—an enzyme that breaks down hexobarbital—in the liver. Consequently, animals who have high levels of this enzyme use up the drug and wake up sooner than animals who do not break it down as readily.

"It's not a matter of one kind of bedding being better than another," he says. "But when scientists report results they should include this kind of information because environmental factors have to be taken into account in any valid evaluation."

Dr. John J. Burns of Hoffmann-La Roche, Inc., Nutley, N.J., also reported on environmental factors and species differences affecting drug action. Insecticides such as chlordane and DDT that are often sprayed in animal rooms significantly affect the rate at which animals metabolize drugs. Dogs are particularly susceptible to insecticides, he says. Dr. Burns' studies also cast doubt on the belief that monkeys' response to drugs is most indicative of man's reactions. In some cases, the monkey is really predicative of what will happen in the dog, not in man, he found. He tested the time it takes for man, monkey and dog to metabolize antipyrine, a fever-reducing drug, and discovered that man needs 12 hours to do what monkeys and dogs do in less than two hours. Generalizations about ideal animal models are crumbling, and as they fall, complex and unanswerable questions are being raised about the nature of animal data researchers submit to the Food and Drug Administration for evaluation in new drug applications. "At FDA and in industry levels of understanding are going up," Dr. Burns believes.

The intricacies of evaluating drug behavior in animals are outweighed only by the intricacies of applying new insights to drug response in man. "An allergic reaction to simple chemical drugs involves a sequence of several events," Dr. Bernard B. Levine of New York University School of Medicine told the meeting. And this sequence, involving hundreds of separate events at the molecular level, is probably genetically controlled. The number of effects at work in drug sensitivity is so enormous, scientists can only begin to appreciate the dimensions of the task that lies ahead. "We have no simple formula or hypothesis to apply to genetic effects on drug behavior and man's mind is simply not equipped to handle all the varied, specific information at hand," Dr. Levine said. So far, the best doctors can do is assume that if a rare drug allergy turns up in one patient, it may turn up again in some member of the family.

The hope expressed by participants at the symposium is that pharmacogeneticists will eventually clearly recognize the causes of drug allergies in order to prevent toxic reactions, or at least alleviate their sting. ◈