DNA committee has its critics

AN international group of scientists involved in bacteriophage work is unhappy about the way in which the Recombinant DNA Molecule Program Advisory Committee is handling the problems of plasmid engineering, and a meeting of the committee planned for this month has been put off until December because of the concern which has been expressed about its last meeting at Woods Hole.

The group, which consists of 48 scientists who attended the recent Cold Spring Harbor bacteriophage meeting, has sent a petition to the National Institutes of Health (NIH), complaining that the Woods Hole guidelines on recombinant DNA represent a watering down of the recommendations made at the Asilomar conference earlier this year. The Asilomar conference, convened by Professor Paul Berg, was the first gathering of workers in the field to discuss the potential dangers of plasmid engineering, and a subsequent meeting of UK workers at Oxford broadly confirmed the working rules suggested at Asilomar.

In a letter to Dr Dewitt Stetten, Deputy Director for Science, Office of the Director, NIH, the Cold Spring Harbor people complain that a draft of the Woods Hole meeting called "Current Guidelines for Research on Recombinant DNA Molecules" appears "to lower substantially the safety standards set and accepted by the scientific community as represented at the meeting at Asilomar in February, 1975".

The letter "strongly requests" that the advisory committee considers at its postponed meeting the feelings of the group in three areas.

- They urge that the most hazardous experiments be curtailed until some experimental determination of the risks inherent in such procedures is made. They say, for instance, that the extent of containment possible with different vectors remains to be shown.
- They are concerned that any mammallian DNA (let alone animal viral DNA) can, by the present draft, be cloned under less than P3 containment, and they say that they are not persuaded that an untested vector designed for safety reasons is by itself an adequate safeguard for such experiments in an open laboratory. They add that "strong consideration should be given to limiting shotgun experiments of mammalian DNA to P4 containment until proven safety vectors are available".
- They feel that the composition of the committee should be broadened to include more representation from the areas of animal virology, plant pathology and genetics, and epidemiology; and also that the advisory committee should have much stronger representation from scientists not directly involved in cloning experiments. And taking a line which the committee will surely find hard to swallow, they think it advisable "to consider representation of the public at large".

One of the organisers of the petition, Richard N. Goldstein, of the Harvard Medical School, says the letter "reflects a deep concern" with the results of the Woods Hole meeting, and he believes it is "exceedingly important that the general scientific community be made aware of these developments".

- This week Dr Goldstein reported that the Woods Hole guidelines had been scrapped. According to Goldstein, Dr Betty Kutter, "a vocal critic of these guidelines and a member of the Recombinant DNA Molecule Committee, has been charged with the rewriting of these guidelines as a result of the pressure put on the committee by many dissatisfied scientists".

Trials for Laetrile

by Colin Norman, Washington

EVER since the days when medicine was largely the province of hucksters and snake oil merchants, people have been touting cures for cancer. Nowadays, such cures may be mentioned briefly in a racy tabloid newspaper, but they are usually ignored by self-respecting scientists, attract mercifully little following, and are quickly forgotten. But not so with one purported anti-cancer remedy called Laetrile.

Although declared contraband by the federal government, outlawed by several state governments and found to be utterly worthless in a number of tests carried out at several prestigious cancer research institutes, Laetrile is now being consumed by an estimated 20,000 people in the United States. It is available on the black market, or through clinics in Mexico and West Germany, to which desperate American cancer sufferers are flocking in droves. It owes its popularity in the United States to a vocal, and at times heated, campaign by a number of groups on the West Coast who are fighting to get legal restrictions on Laetrile lifted.

The bitter battle over Laetrile would have all the ingredients of a good thriller, if the subject matter were not so tragic. Research reports have been stolen and given wide publicity, an international smuggling ring has been broken up by federal agents, cancer researchers have been accused of deliberately suppressing information, numerous court fights have occurred, and right-wing political groups have been accusing the government of invading personal freedom. The matter has certainly caused a headache for the Food and Drug Administration and the National Cancer Institute, and a good deal of embarrassment for the Memorial Sloan–Kettering Cancer Center in New York.

Laetrile was apparently first used for cancer treatment in the 1920s by a California doctor called Ernest T. Krebs, Sr, but it was too toxic to be much use. A purified form was developed in 1951 by Krebs' son, E. T. Krebs, Jr, a biochemist, who claimed that the substance was safe for injection. More recently, Laetrile has been produced in a form which can be taken orally, and its use has skyrocketed.

There have been numerous anecdotal reports of cancer sufferers who have gone into remission after taking Laetrile, or who have at least experienced a cessation of pain and have died in relative peace. But there have been no formal, clinical trials to test the efficacy of the substance, and until recently there have been few animal trials to test Laetrile's purported anti-cancer activity. Results of two extensive animal trials will, however, be published later this month. They are unambiguously and crushingly negative.

Proponents of Laetrile have even suggested an elaborate mechanism to explain its alleged action. The substance, they suggest, is broken down inside cancer cells by the enzyme β-glucosidase, to release benzaldehyde and hydrogen cyanide in sufficient quantities to kill the malignant cells. Normal cells, they suggest, are protected because they contain the enzyme rhodanese which, in the presence of thiosulphate, converts hydrogen cyanide to the less toxic thiocynate. It is a neat mechanism which every cancer chemotherapist looks for—something which is entirely specific to cancer cells but non-toxic to normal cells. The trouble is, though, that there is not a shred of evidence so far to support it.

The campaign in support af Laetrile certainly has considerable popular appeal. A film developed for the pro-Laetrile forces, for example, begins with the following statement: "This year, 250,000 Americans will die from cancer ... this great human tragedy can be stopped now entirely on the basis of existing scientific knowledge". It goes on to note that "the history of science is the history of struggle

against entrenched error", and that some of the greatest scientists were ridiculed in their own time. It states that "with billions of dollars spent each year on research, with other billions taken in from the cancer-related sale of drugs, and with vote-hungry politicians promising ever increasing government programs, we find that, today, there are more people making a living from cancer than are dying from it", and argues that scientists therefore don't really want to find a cure for cancer because "if the riddle were solved by a simple vitamin [Laetrile], this giant commercial and political industry could be wiped out overnight".

In 1972 and 1973, the campaign took a new tack. Petitions, said to be signed by 43,000 people, were sent to former President Nixon demanding that clinical trials be run on Laetrile to test its anti-cancer properties. The petitions were responsible for launching four animal studies: two were carried out under contract to the National Cancer Institute (NCI), and two others were performed at the Memorial Sloan–Kettering Cancer Center and the Catholic Medical Center in Queens, New York.

Results of the two NCI studies will be reported later this month in the September/October issue of *Cancer Chemotherapy Reports,* a journal published by the NCI. Conducted by Isidore Wodinsky and Joseph Swiniarski at Arthur D. Little Inc. (ADL) in Cambridge, Massachustts, and by W. R. Laster, Jr, and F. M. Schabel, Jr, at the Southern Research Institute (SRI) in Birmingham, Alabama, the studies involved large doses of Laetrile administered to mice bearing transplanted tumours. A standard method of screening for anti-cancer drugs, it consists of transplanting pieces of tumour from one mouse into other, genetically identical, mice and observing the effects of drugs on tumour growth. The ADL studies involved four different types of cancer, and the SRI tests three.

According to Wodinsky and Swiniarsky, Laetrile did not prolong the life span of mice bearing any of the transplanted tumours, even at doses close to the level at which the substance was found to be toxic. They therefore conclude that "no anti-tumour activity was found in any of the four systems tested". Similar results were reported on the basis of the SRI tests. Laster and Schabel conclude that Laetrile "did not demonstrate significant anti-tumour activity against any of these three tumour systems".

Such negative results would normally be sufficient to close the book on a possible anti-cancer agent, but not Laetrile. The studies at the Sloan–Kettering have, inadvertantly, provided some ammunition for the pro-Laetrile forces.

According to Dr C. Chester Stock, a vice-president of Sloan–Kettering, and director of the institute's Walker Laboratories, his institute took a brief look at Laetrile in the early 1950s, but found no effect when it was tested against one implanted tumour system. The work was then dropped because "other agents were showing promising activity", he said. But when the petitions started flooding into the White House and letters began arriving at the Sloan–Kettering, demanding that Laetrile be tested, it was decided that the institute should take a second look at the substance. Particularly pertinent to that decision was the fact that the chairman of the President's Cancer Panel, Benno C. Schmidt, is also a board member of the Sloan–Kettering Institute (SKI). According to Stock, tests were run on "a battery of transplanted tumours" at high doses, in 1972, but he said "we didn't see any benefit whatsoever"—Laetrile again proved to be ineffective as an anti-tumour agent.

Although the use of transplanted tumours is a standard procedure for testing anti-cancer drugs, it has recently come under considerable criticism on the grounds that transplanted tumours may not behave like spontaneously occurring ones. The decision was therefore made at the SKI to test Laetrile on a strain of mice (developed by Dr Daniel Martin at the Catholic Medical Centre) which has a very high incidence of spontaneous mammary tumours. The tests were begun in 1972 by one of the SKI's most venerable researchers, K a n e m a t s u Sugiura.

Sugiura's initial studies seemed to show a surprising effect. Although Laetrile apparently had only a small and variable effect on the primary tumours, it seemed to have a marked effect on the appearance of lung metastases. According to tests run between September 1972 and June 1973, Sugiura found that whereas 78% of the mice in control groups had lung metastases present, only 17% of those treated with Laetrile developed metastases. Sugiura wrote up the results of his experiments in a report which he circulated to his colleagues.

In the autumn of 1973, somebody at the SKI sent a copy of Sugiura's report to Laetrile proponents on the West Coast, and it subsequently got banner headline treatment. Supporters of Laetrile began to claim that the prestigious Sloan–Kettering Institute had proven the effectiveness of Laetrile, and that the institute was suppressing the results.

Since that time, Sugiura has continued to study the effect of Laetrile on spontaneous mammary tumours in the mice bred by Martin, and parallel tests have been run by two other researchers at the SKI and by Martin himself. Sugiura has continued to find that Laetrile seems to inhibit the formation of lung metastases, but the other three investigators have all come up with negative results. Reports of Sugiura's recent research have been circulated within the SKI, and a month or two ago they were again leaked to Laetrile proponents on the West Coast, who distributed them widely to the general press.

In view of the wide publicity which the studies have received, and the charges that the SKI has been suppressing results favourable to Laetrile, Dr Stock recently discussed the issue.

Stock said that "because of the emotion surrounding this issue, we felt that we should be cautious". It was agreed that Sugiura and Martin should cooperate in a test on Laetrile in mid-1974. The experiment proceeded in exactly the same manner as Sugiura's earlier studies, except that lungs from the mice were subjected both to microscopic examination and to bioassay—the lungs were transplanted into a fresh animal to see whether tumours grew. Bioassay provides an objective assessment of whether or not lung metastases were present. The results proved negative—there was no difference between mice treated with Laetrile and the controls. Similarly, Stock said that the two other SKI studies proved to be negative.

Thomas emphasised that the SKI has certainly made no attempt to suppress results favourable to Laetrile, and he said that "I think it is safe to say that if it had been any other agent under study, we would have lost interest in it" when Sugiura's early results seemed to indicate that it had little or no effect on primary tumours.

The fact remains, however, that in spite of a large, and growing, body of information which indicates that Laetrile has no anti-tumour effect in animal systems, the substance is continuing to grow in popularity, and its proponents remain convinced of its efficacy. They are still demanding that human trials should take place.

Most cancer specialists are adamant that clinical trials are certainly not justified. Thomas, for example, said that "in the absence of positive data from animal experiments, use of Laetrile in human beings with cancer remains extremely difficult to justify, particularly in patients with cancers that are treatable by surgery, radiotherapy or chemotherapy". The Food and Drug Administration (FDA), which would have to licence any clinical trials, agrees. An FDA official pointed out that it would be difficult to

Waste line

KENNETH MELLANBY

IT is not, I hope, a serious contravention of the Official Secrets Act to reveal that, in Committee Room 11 in the Houses of Parliament, the wall above the rostrum is adorned with an enormous oil painting which depicts "The Speakers Procession in 1884". The Parliamentary and Scientific Committee sometimes meets in this room, and when the proceedings are less than enthralling I find myself studying the picture. My interest is not so much in attempting to identify the impressive figures (the print on the key diagram is too small to be read at a distance) as in wondering at the appalling mess of litter and waste paper through which the procession is wading. It is almost like the platform of a London underground railway station in 1975. I am glad to say that the corridors of power are, in this respect, more hygienic today, if other places are becoming filthier.

Litter and refuse are undoubtedly providing some of our most difficult pollution problems today. Both New York and London seem to be permanently subject to piles of stinking refuse, even when there is no industrial dispute between the local authorities and the refuse collectors. Earlier this year the strike of dustcart operators in Glasgow faced the city with a serious public health problem, so that the army had to be called in to clear away the more noisesome dumps. The problem is made worse by the way in which the bulk of the litter is swelled by masses of unnecessary packing material, but its danger is also a function of affluence, for it is the waste food, much of it initially quite fit for consumption, that makes refuse a public health problem, attracting rats and increasing the risk of transmission of disease.

What may not be generally realised is that it is the successful control of air pollution which exacerbates the problem. Earlier this century the volume of refuse was much smaller, partly because much was burned on domestic grates and kitchen ranges.

It is true that some of the more affluent do have refuse disposal units, to pulverise food and some other wastes, which are then discharged into the sewers. This may allow their hygienic disposal, though there have been reports from America of a consequent overload of sewage works and even more serious pollution of rivers when the material is discharged, untreated, into them. We are often better at moving pollution from one place to another than in curing or controlling it.

The Chief Scientist to the Ministry of Agriculture, Fisheries and Food, has recently stated that, of the food bought in Britain, as much as a quarter may be wasted. This does not include the substantial amount that is eaten, over and above their actual requirements, by most of our population, contributing to the obesity which is the most serious symptom of malnutrition in most Western countries today. It seems likely that, if we eliminated waste and gluttony, we could reduce our balance of payments deficit by nearly £1,000 million, without any marked change in our feeding habits.

Although there is a growing interest in recycling all types of waste material, little food is re-used in this way. In the past, much pig swill came from hotels, schools and even from private houses. Since swine vesicular disease has become a serious problem, such collections of swill have greatly decreased, as regulations to ensure that the food is properly treated and sterilised, though wise and necessary, are too stringent for the majority of small operators. It is calculated that the dustbins of Britain contain at least 3 million tons of "putrescible material" (the trade jargon for waste food) a year, much with a high protein content, and that if this were properly treated it could feed more than 1 million pigs—as well as reducing the health risks arising from uncollected refuse.

If waste food is to be used to feed animals, it has to be separated and treated. There are less difficulties in recycling refuse as a soil fertiliser or conditioner. Considerable amounts of sewage sludge are used in this way, and several cities have installed elaborate and expensive plant to produce municipal compost. Wastes brought in by the dustcarts are sorted and separated (tins and iron scrap is removed magnetically, baled and sold) and the remainder, with added sewage sludge, goes through a digestive process. The end product is a brown powder which is quite pleasant to handle. It contains a significant amount of nutritive salts, and is an excellent conditioner for intractable clay soils. Although available at a low cost, most farmers have been reluctant to use municipal compost, because it usually contains substantial amounts of heavy metals, the lead level commonly exceeding 200 p.p.m. There is evidence that, in the presence of a high level of organic matter, this lead is hardly taken up by most plants, but it does remain in the soil and might give rise to problems at a later date if the organic level fell substantially.

Waste disposal and re-use is thus seen to be a very complicated problem. Clearly the best solution is to produce less, and to see that what cannot be avoided does not give rise to further problems. But it is at least encouraging that our present Members of Parliament are better house trained than their Victorian predecessors.

design an acceptable clinical trial without depriving patients of other, accepted methods of treatment. In other words, if Laetrile were put on clinical trial, it could only be justified ethically it if were simply added to other forms of treatment, and that wouldn't make for a very rigorous test.

There is, however, another extremely important aspect to the Laetrile debate. Laetrile, in its purified form, is relatively non-toxic. It can be fed to animals in large doses before any adverse effects are noted; according to Thomas, at least one of the "solid pieces of data" to come out of the SKI studies is confirmation of that fact. Laetrile proponents therefore argue that FDA should not regulate the substance as a drug, but as a food or even a vitamin.

Would it do any harm if the FDA were to allow Laetrile to be marketed like any other so-called health food? Even the *New York Times* has suggested, in an editorial published in August, that since Laetrile is usually taken by cancer patients who are beyond help from conventional therapies, they should not be denied even a possible placebo effect from the substance. But a letter from Dr Sherwin Gardner, Deputy Commissioner of the FDA, took exception to that suggestion. Pointing out that the FDA has a duty to protect the public against ineffective drugs, Gardner said he believes that 'the idea of fraudulent promotion and sale of bogus cures to the desperately ill and dying is appalling". It is also argued that, if Laetrile is made more widely available, it will be taken by cancer patients in preference to other therapies which have at least proved effective in the past. □