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INTERNATIONAL CENTRE FOR ENVIRONMENTAL AND INDUSTRIAL TOXICOLOGY (ICEIT)

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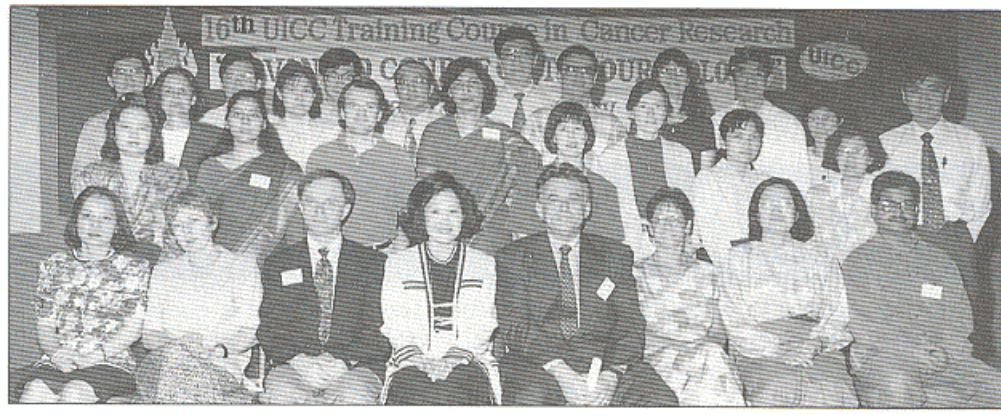
CRI HOSTS 16TH UICC TRAINING COURSE



From 31 January to 11 February 1995, the Chulabhorn Research Institute hosted an international training course on tumour biology at the Institute's Laksi Centre. This advanced course was jointly organized with the International Union Against Cancer (Union Internationale Contre Le Cancer-UICC), with support from the USA's Roswell Park Cancer Institute. It was attended by 22 researchers from 4 countries.

UICC is an international organization funded by its institutional participating members and created to combat cancer through a number of programmes including exchange of scientists, dissemination of information on cancer to lay communities, specific aspects of the disease itself, the epidemiology and prevention of cancer, and also the treatment of cancer. UICC is run by an elected committee appointed from its institutional members which include hospitals, research institutes

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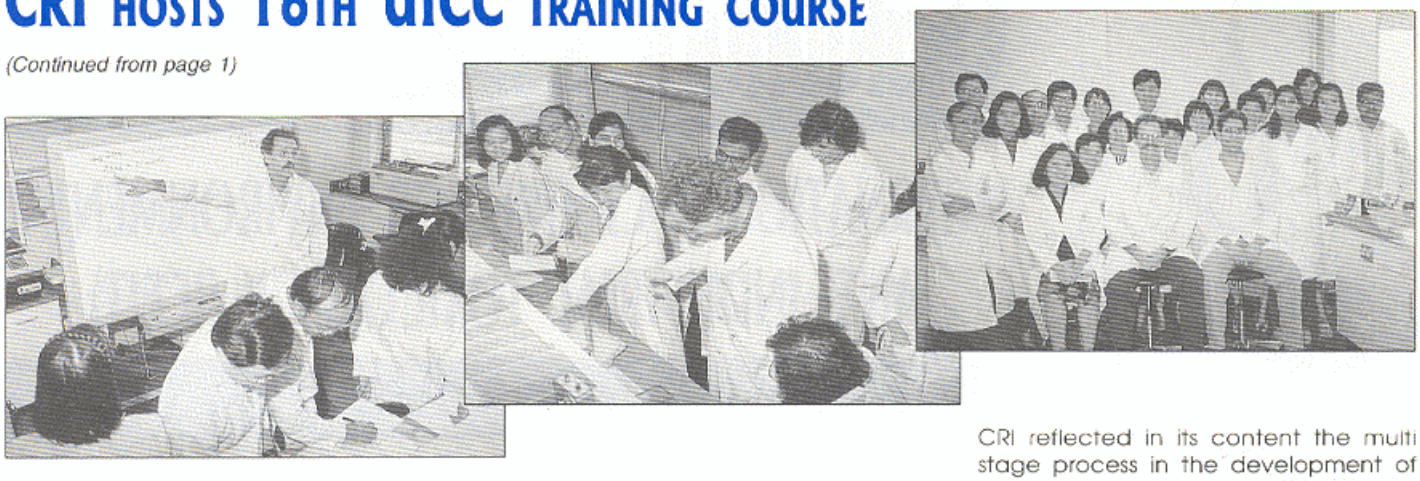

and government departments, representing a world-wide network. A general assembly formulates the policy of all its members. Research, in itself, is not a priority of the UICC. This is carried out by the institutes that are among the participating members. Under the tumour biology programme, two training courses are held each year world-wide. The highly intensive programme of the 12 day advanced course on tumour biology hosted by CRI reflected in its content the multi stage process in the development of cancer. The visiting faculty staff of 14 experts underlined the multi and inter-disciplinary nature of approaches to the understanding of tumour biology. This accounts for the very high cost of running workshops at the necessary level of specialisation.

NTP ANNOUNCES BIOASSAY RESULTS

The National Toxicology Program has presented six more technical reports in its ongoing series of toxicology and carcinogenesis studies. All six reports were approved by the NTP's Board of Scientific Counselors' Technical Reports Subcommittee in a public review held on November 29 1994 at the US National Institute of Environmental Health Sciences. Each report involves a series of long-term studies in which male and female rats and mice were given a range of doses of test chemical followed by extensive histopathologic examination.

Nickel oxide, nickel sulfate, and nickel subsulfide. Three separate studies were performed to evaluate and compare the toxicity and carcinogenicity of three nickel compounds prominent in nickel mining and refining. These studies involved inhalation exposure to atmospheres containing particles of nickel oxide, nickel sulfate hexahydrate, or nickel subsulfide. The three nickel compounds all caused chronic lung inflammation in male and female rats and mice, but the carcinogenic responses varied.

Nickel subsulfide exhibited clear evidence of carcinogenic activity in male and female rats, but not in mice, based on the occurrence of neoplasms in the lung and adrenal gland. Nickel oxide also caused neoplasms at these two sites in male and famale rats and also showed equivocal evidence of carcinogenicity in female mice based on a marginal increase in lung tumors. In contrast, the water-soluble nickel sulfate hexahydrate exhibited no evidence of carcinogenic activity in either rats or mice.

Isobutyl nitrite. Isobutyl nitrite is used in fragrances and is also abused as a euphoric. It was nominated for study to investigate a possible association with the higher incidence of Kaposi's sarcoma among male homosexual AIDS patients (see Haverkos et al., *EHP* 102: 858-861). When animals were exposed to this chemical via inhalation exposure, male and female rats exhibited clear evidence of carcinogenic activity, and male and female mice exhibited some evidence of carcinogenicity, based on increased incidences of lung neoplasms in all four sex/species groups.

Triethanolamine. Triethanolamine is used as a surfactant in a wide variety of industrial and household products, including cosmetics and detergents. When administered by dermal application to rodents, triethanolamine was associated with increased incidences of liver tumors in female mice. Marginal increases in the incidences of liver tumors in male mice and kidney tumors in male rats were judged equivocal.

2,2-Bis (bromomethyl)-1, 3-propanediol. 2, 2-Bis (bromomethyl)-1, 3-propanediol is a brominated fire retardant (trade name FR-1138) used to treat molded plastics and polyurethane foam. When given in feed, this chemical was clearly carcinogenic to a variety of organs in male and female rats and mice, including at least 14 distinct tissue sites in male rats.

Source: Environmental Health Perspectives, Vol. 103, Number 2, February 1995.

Protein Studies of Alzheimer's Tangles

Alzheimer's tangles, the twisted filaments which scar the brain of Alzheimer's victims, are one of the two major pathological features of the disease. Many researchers have concentrated their efforts on the other major Alzheimer's feature, the plaques, which contain a potentially neurotoxic protein called ß- amyloid. However, some recent studies are focusing on neurofibrillary tangles and the ways in which they might contribute to neuronal death. These research studies suggest that an important factor involved in the tangles is an abnormal form of a protein called tau. This explanation is based on experiments which indicate that phosphatases, enzymes that remove phosphate groups from tau, are suppressed in the neurons of Alzheimer's victims.

Carrying more phosphates than it should keeps the protein from performing its normal role of securing vital parts of the neuronal cytoskeleton and thus harms the cell. Tau's ties to Alzheimer's were highlighted in 1991, when Trojanowski and Lee showed it made up the paired helical filaments (PHFs) that comprise the neurofibrillary tangles. They also found that "PHF-tau" carries many more phosphate groups than cover the normal protein, including many at sites not ordinarily phosphorylated (Science, 8 February 1991, p. 675).

Animal studies indicated that extra phosphates might lead to neuronal damage, even before tangles form, by interfering with a crucial function of tau. The protein is supposed to assemble and stabilize the microtubules, filaments that convey cell organelles, glycoproteins, and other vital materials through the neuron. Tau's ability to bind to microtubule segments is partly determined by the number of phosphate groups attached to it. Extra phosphates might derail this process.

These ideas spurred a search for the mechanisms that change normal tau into PHF-tau. Researchers turned first to kinases, enzymes that add phosphate groups to proteins. But no one could definitively catch a particular overactive kinase in the act.

In recent experiments carried out by researchers at the University of Pennsylvania School of Medicine, the phosphorylation state of tau taken from the brains of epileptic but otherwise normal surgical patients was mapped. The analyses showed that tau in living neurons possesses phosphate groups at many of the same sites as PHF-tau. But after progressively longer postsurgical intervals, tau lost more and more phosphates. This indicated that the phosphatases were still functioning in cells from normal brains. PHF-tau in Alzheimer's brains, in contrast, remains phosphorylated many hours after death.

This suggests that phosphatases are underproduced in the diseased neurons or that their action is somehow being inhibited, thus impeding PHF-tau's ability to fasten microtubules. The neurons ultimately die and leave behind "ghost" tangles.

Researchers believe that once formed into tangles, the masses of PHF-tau further obstruct cellular transport and damage the neuron.

The important question is what prevents protein digesting enzymes from eliminating them? A recent study points to aluminium as a possible factor. Researchers injected the brains of a group of rats with a combination of human PHF-tau and aluminium salts. They compared the brains of these animals with those from rodents injected with PHF-tau and one of several other proteins associated with Alzheimer's disease, including ApoE4 and ß-amyloid. (Duke University's Allen Roses has argued that ApoE4 contributes to the hyperphosphorylation of tau.) The scientists found that PHF-tau injected along with aluminium resisted breakdown for the longest period. The researchers suggest that aluminium, which binds avidly to phosphate groups, may change PHF-tau's molecular conformation so that it is less accessible to the protein digesting enzymes.

The activity of aluminium may thus be "the crucial step" opening the route to tangle formation.

Other scientists, however, say the "crucial step" may occur even earlier, before phosphatases or aluminium come into play. In the first place, no one knows whether the modest build-ups of aluminium found in the brains of Alzheimer's patients contribute to, cause, or result from tangle formation.

However, both tangles and plaques apparently result from breakdowns in the balance between protein synthesis and degradation in the neuron, and the new findings may point to a common path during at least part of this process. And perhaps along that common path will lie a way to untangle the puzzle of the disease.

Source: Science, Vol. 267, 10 February 1995.

NEUROGENIC SWITCHING

There are two interrelated systems by which foreign materials can produce inflammation in a tissue. Immunogenic inflammation arises when an antigen binds to an antibody or leukocyte receptor to trigger an inflammatory cascade. Prior sensitization is required, and the inflammatory response can take several forms including immediate and cell-mediated hypersensitivity. Neurogenic inflammation occurs when a chemical combines with the chemical irritant receptors on sensory nerves, leading to the release of substance P and other inflammatory neuropeptides. Neurogenic inflammation can also arise when a nerve impulse travels down an axon to release substance P at the terminus. There is an interplay between immunogenic and neurogenic inflammation, in that substance P can degranulate mast cells, and histamine can activate sensory nerves.

One puzzling feature of the inflammatory response is that a stimulus in one tissue can sometimes lead to inflammation at another site. Food allergy provides an example. Ingesting of a food allergen can produce gastrointestinal symptoms, with diarrhea, abdominal pain, bloating, and emesis arising from the direct degranulation of gut mast cells with local mediator release.

Food hypersensitivity can also manifest as arthritis and migraine. Histamine from gut mast cells could bind to sensory nerves to produce an afferent signal, which could be rerouted via

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DR. R. BRENTANI

Chairman of UICC's Tumour Biology Programme Evaluates The International Advanced Training Course on Tumour Biology

When interviewed by the Newsletter Editor, Dr. Brentani, Chairman of UICC's tumour biology programme and one of the visiting faculty staff, firstly expressed UICC's gratitude to HRH Princess Chulabhorn for accepting to hold the training course at CRI and to generously contribute to the costs of the workshop. In Dr. Brentani's view: "CRI must be commended on the quality of its staff and the excellence of its laboratory facilities. Both these factors have made a most important contribution to the success of the course".

Hands-on laboratory experience is an essential component in a training course that aims to familiarise researchers with the most up to date developments in tumour biology. "Basically, this kind of course permits us to cover the full complexity of tumour biology in a way that will prepare participants to apply theory to practice."

The selection of participants who applied to take the course was the responsibility of Dr. Mathuros Ruchirawat, Vice-president for Research at CRI, based on guidelines provided by UICC. Dr. Brentani commented that he had been very favourably impressed by the quality of the 22 participants. Because of the high level of their past experience, they had been able to benefit from the specialised nature of the course. He had received very positive feedback from the participants on the value of the course to their own research development.

In discussing the importance of research in tumour biology, Dr. Brentani stated: "With improvements in the standard of living in most countries, infectious diseases will be greatly reduced by the end of the century. People will live longer and therefore diseases involving cancer will have a higher incidence. Research into cancer is, therefore, of the greatest importance. Without an understanding of how tumours develop, effective treatment is impossible. At present, physicians do not really understand the basics. It is difficult to treat something that you do not understand. If cancer could be treated simply by cutting out a tumour, it would be a simple matter; but when cancer reoccurs, surgery clearly is not the answer. We need to understand the processes by which cancer occurs in order to know how it can be treated. Unfortunately, insufficient priority is given to cancer research; in developing countries, in particular, government priorities lie elsewhere."

This is one reason why it is important to organise training courses regionally so that the high costs can be justified in terms of maximum outreach effect. Also, the training needs of developing countries are different from those of developed countries which have the resources to approach research in a highly specific way.

Dr. Brentani illustrated this point with the example of his own career in medical research: "In terms of differences between developing and developed countries, I think I am a good example of the value of these kinds of endeavour. Essentially, I never left Brazil to get my medical training. I got all my experience at home. I only went international in 1975, through an initiative such as the training course that we have been running here. As soon as I entered medical school at the University of Sao Paulo, Brazil, I was attracted to research. Before I graduated I had already published three papers in creditable journals, without ever having had international exposure. Then, after I graduated, I made the decision not to go to the United States to study for my Ph.D. at the Rockefeller Foundation where I had been offered a scholarship. This was a difficult decision, but one which I have never regretted. If I had left, I would not have been able to continue with the research that I had started at the University of Sao Paulo. This initial research was in renophysiology. I only started working in cancer research in 1972. For me, science is of essential importance. You can feel gratified even though the financial rewards are in no way commensurate with the hard work involved. What you are doing as a researcher is capable of worldwide recognition even though you are in the back woods."

The facilities of the Chulabhorn Research Institute have enabled UICC to demonstrate the value of such an endeavour, and to further inspire participating researchers from the region through the benefits of the highest quality of training in tumour biology.

HORMONES IN FOOD

The endocrine system produces hormones that play crucial roles in reproduction, development, and metabolism. However, fish, wildlife, and humans consume food and water containing environmental toxicants that behave like hormones and have the ability to cause effects, sometimes irreversible, ranging from sterility and abnormal sex differentiation to cancer. Pregnant women exposed to these substances can transfer the effects to their fetuses.

Several environmental chemicals mimic or interfere with female and male hormones, thereby impairing reproduction and growth. One of the first major breakthroughs was the discovery of vaginal cancer and other problems in the sex organs of daughters of women who received DES (diethylstilbestrol), a drug prescribed to prevent spontaneous abortions, from 1948 to 1971. Laboratory experiments demonstrated these same effects in female animals and others in male animals. Later, human studies discovered comparable effects in the sons of DES-exposed mothers.

An early sign that environmental chemicals might impair endocrine function was the discovery in the 1950s that DDT caused birds such as sea gulls and bald eagles to lay eggs with thin shells, with the result that many embryos were crushed to death. In addition, reproduction in gull colonies heavily exposed to DDT began to decline precipitously in the late 1960s, apparently because in some cases two females, instead of a male and female, were sharing nests, and the young in the communities had grossly feminized reproductive organs.

Another sign that environmental hormones may adversely affect sexual development in the human population is the decline in sperm counts and semen volume in men over the past 50 years. In one study of 14,947 men, the sperm count dropped by almost 50% between 1940 and 1990, and the amount of semen the men were able to produce dropped an average of almost 20%. Estrogenic compounds loom as a major problem. They include the organohalogen pesticide DDT and its major metabolite, DDE, which accumulate in body fat and are found in breast milk; hydroxylated forms of polychlorinated biphenyls (PCBs), used as pesticides and in electrical components, which also accumulate in body fat and have been found in fish; *p*-nonyl-phenol and bisphenol-A, which are released from some plastics under various conditions. Bisphenol-A is also involved in detergent manufacturing and has been linked to feminization of fish species in England.

Dioxins and dibenzofurans are another group of hormone-like contaminants. In laboratory animals, they modify a broad array of hormones, including estrogens. Waste products of industrial processes, these chemicals have been found in meat, dairy products, and fish oil.

Some environmental compounds resemble male hormones. One example is vinclozolin, a fungicide used on fruits and vegetables, which interferes with the performance of male sex hormones. When a pregnant rat is exposed to high doses of vinclozolin during embryonic development, males are born without a penis or with other malformations of sex organs.

Although individual exposures to all chemicals vary with socioeconomic, nutritional, and health status, everyone is exposed to a certain, perhaps dangerous, level of environmental hormones. Environmental hormones infiltrate food and water in places remote from the site of original release because chemicals are carried as particulates or gases in the air, surface waters, groundwater, and ocean currents across or between continents. Contaminated animals also travel great distances. Many environmental hormones accumulate in animal fat, becoming progressively concentrated in animals high up in the food chain. For instance, salmon eaten by humans may contain relatively high amounts of PCBs or dioxins in its body fat.

Many chemicals persist in the environment. At one time, 15 chemicals similar to DDT and PCBs were registered in the United States; now there are 4, but only one of these, endosulfan, has a number of food uses.

Consumer advocates fault the EPA's current method of assessing pesticide safety because it fails to address cumulative risk. The agency does not know which pesticides are used on particular foods, and it does not physically test all the combinations of pesticides to which a person may be exposed.

Regulatory agencies are often forced to look at chemicals in isolation. However, many chemicals have competing or exacerbating actions, many of which have not been identified. Hormones also have widely varying activities within different cell types; for example, some chemicals may function like estrogen in breast cells but are antiestrogenic in liver cells. All of these factors make it difficult to assess the overall impact on human health from exposure to environmental hormones.

Source: Environmental Health Perspectives, Volume 102, Number 8, August 1994.

Xeno-oestrogens and Male Fertility

Xeno-oestrogens are environmental chemicals that mimic the actions of the predominantly female hormone oestrogen. There is evidence that these chemicals, which are widely used in industry and agriculture, adversely affect the developing male fetus and result in a decline in male fertility. The suggestion that oestrogens could have an important role in male reproductive health came from observations of reproductive tract disorders such as undescended testicles and hypospadias observed in male children of women who had been given the synthetic oestrogen stilboestrol to prevent miscarriage.

An article published in *The Lancet*,* Professor Skakkebaek of the University Department of Growth and Reproduction in Copenhagen, Denmark, and Dr. Richard Sharpe from the Medical Research Council Unit of Reproductive Biology in Edinburgh, UK, suggested that the growing evidence of reproductive abnormalities in the human male is related to exposure to high amounts of oestrogen while the fetus is developing in the womb.

The same researchers have made more recent claims that the most likely source for exogenous oestrogens is environmental pollution due to organochlorine pesticides (including DDT and the related compounds Aldrin and dieldrin) PCBs, dioxins, furans and other synthetic chemicals released into the environment during the past fifty years. A major problem with man-made chemicals is that they are likely to remain in the environment for a considerable time since they are resistant to biodegradation and tend to become concentrated in body fat. DDT, which was widely used until it was banned, in many countries, in the 1960s, degrades very slowly.

More research is needed into the reasons why external oestrogens inpair fetal development and affect sperm count in later life. Because of the critical period when xeno-oestrogens act and the duration of maternal exposure, the important factor is not necessarily the amount of pollutant exposure during pregnancy but the amount of exposure during the woman's life time.

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* The Lancet 341: 1392-1395 (1993)

Assessing Human Health Risks From Exposure to Chemical Mixtures

Exposure at different levels to large numbers of chemical compounds is now a global environmental reality. Mixtures of chemicals are ubiquitous in ground and surface water, in our air, food, and drinking water, as well as in soil surrounding toxic waste disposal sites.

Despite the potential for exposure to environmental mixtures, the great majority of established exposure standards are for single compounds. Some researchers are reluctant to undertake research on health risks related to chemical mixtures, arguing that it is difficult enough to address all the uncertainties associated with single chemical risk assessment.

Basic to the study of chemical mixtures is the issue of what approach to take. A bottom-up approach is typically aimed at identifying mechanistic interactions of simple mixtures to predict their effects. Top-down studies, on the other hand, examine the effects of complex mixtures to determine the underlying mechanisms. However both approaches are subject to some criticism. There are simply too many mixtures and multiple chemical exposures in the environment for toxicity assessment by itself to be a viable approach.

Moreover, inconsistent usage of some key terms within the literature on toxicology has made communication of findings on chemical mixtures problematic. This is especially true in fields such as toxicology and biostatistics where there has been lack of agreement over the precise meaning of terms.

A recent proposal has been the definition of three fundamental classes of joint interaction of chemicals:

- Additivity – the effect of a combination is exactly what is expected. For example, the combination of one chemical with a toxicity level of 1, with another compound also having a toxicity of 1 would equal a toxicity level of 2. This general classification of additivity implies nothing about how the addition occurs.
- Synergy – a positive interaction such that the response is greater than expected. Simply put, a combination of two compounds with individual toxicity levels of 1 might yield a toxicity level of 10, for example.
- Antagonism – a negative interaction such that the response is less than expected. Here, the mixture of two compounds with a toxicity level of 1 each might give a toxicity level of 1.5.

Within organisms, chemicals can interact at a number of different levels, through absorption, metabolism, distribution, and at the site of action. Rather than refer to chemical interactions strictly in terms of additivity, synergy, or antagonism, some researchers prefer to use the terms "pharmacokinetic" and "pharmacodynamic" interactions. Pharmacokinetic interactions are when the tissue dose of a chemical per unit of exposure is altered by co-exposure to another chemical. A pharmacodynamic interaction is when tissue responses to a unit concentration of the chemical is altered due to co-exposure to other chemicals.

Through animal models of pharmacokinetic interactions of specific chemical compounds, scientists hope to make predictions for occupational exposure, leading to improved regulatory standards for work-place safety. For example, there are experiments that simulate human exposures to atmospheric mixtures of styrene and butadiene (a probable human carcinogen, according to the EPA) that may occur during processing and production of styrene – butadiene polymers. In one such study, toxicologists led by Gyorgy A. Csanady at GSF Institut fur Toxikologie in Neuherberg, Germany, found the amount of butadiene metabolized was inhibited by simultaneous exposure to styrene, whereas butadiene had no detectable effect on the kinetics of styrene. Findings of antagonistic metabolic interactions between these compounds have also been reported by toxicologists at the Chemical Industry Institute of Toxicology. At CIIT, inhibition of the oxidative metabolism of butadiene as well as inhibition of further oxidation and detoxification of an important reactive metabolite has been shown. This metabolite, butadiene monoepoxide, is thought to be partly responsible for the genotoxicity of butadiene.

An approach to improving the assessment of potential hazard for complex chemical mixtures still under development is the use of toxic equivalency factors (TEFs). The use of TEFs involves development of a potency ranking scheme which relies on existing data and scientific judgment. The TEF is derived by observing the data available for one chemical, by looking at the dose-response characteristics for that compound, and comparing it to the dose-response characteristics observed for a prototypical compound. Thus, each chemical in a mixture has a TEF assigned to it.

What is in the future for risk assessment of chemical mixtures? At the EPA's Health Effects Research Laboratory symposium on chemical mixtures and risk assessment in November, William Greco of the Roswell Park Cancer Institute, USA predicted, "By the beginning of the next millennium, routine assessment of the effects of chemical mixtures, for both toxic and therapeutic agents, will be very different from approaches commonly used today."

The future paradigm may well include assays that are more automated and robotized; routine study of multicomponent mixtures; empirical models that will routinely fit to data with sophisticated user-friendly software on fast, inexpensive computer workstations; insightful computerbased graphical exploratory analysis procedures; routine combined pharmacokinetic – pharmacodynamic modeling of chemical mixtures, and standardization of nomenclature and approaches.

Source: Environmental Health Perspectives, Vol. 103, No. 2, February 1995.

"Tiger Team" Probes Computer Systems

Hackers, who illicitly enter computer networks to tamper with data, pose a serious threat to network systems. In response to this threat, the Computer Security Technology Center at Lawrence Livermore National Laboratory has formed a "tiger team" whose job is to probe for weaknesses in computer systems.

The team is currently engaged in attacking the computers at the National Library of Medicine (NLM) in order to test the barriers that NLM has erected to protect the integrity of databases which are extensively used by scientists worldwide.

If hackers succeeded in penetrating the computer system's defences, they could tamper with vital information such as that from MEDLINE, the widely used medical bibliographic database, on GenBank, the database that collects DNA sequences deciphered by geneticists around the world. Such tampering could have disastrous effects on the work of thousands of scientists.

The security exercise at NLM demonstrates how concerned organisations have become about their vulnerability to hackers. The danger is increasing as Internet becomes even more tightly interwoven with scientific research. Large scientific databases are accessed and updated every day via the Internet. Researchers use the net to collaborate, send out papers and exchange data.

Although most e-mail accounts, databases, and local networks are officially secure – unaccessible without a password – hackers have many methods of attack, from exploiting software weaknesses to stealing passwords.

Overall statistics on hacking incidents are impossible to ascertain, but some universities estimate between 10 to 30 attempts a week.

One US university, Texas A & M, has reacted to hackers by setting up a security fire wall to shield its internal network. A fire wall allows computer traffic to pass only via certain restricted gateways, consisting of computers and filtering programs. Generally, users inside the fire wall can reach the outside world easily, but outsiders trying to gain access to the organisation's network face impediments. One kind of fire wall relies on packet filters. These systems block packets of information of allow them through depending on what computer they come from or the kind of service they are seeking on the destination computer.

Another type of fire wall allows access to more services but monitors each stream of packets closely by funnelling it through a separate application-level gateway for each Internet service such as telnet, ftp, or e-mail. So far, however, gateways cannot reproduce the freedom of open Internet access.

Many government centers make access easier for outside users by setting up their computer resources so that outsiders need not pass through filters and gateways. The National Center for Biotechnology Information (NCBI), which runs GenBank, places the computer that acts as the GenBank server to the world outside its fire wall. The archive copy of the database is kept on NCBI internal machines, to which the outside world has no access.

However, security problems at universities can be even more acute than at government institutes because their computer systems are managed more loosely. Thanks to inexpensive desktop computing power, most departmental research groups have their own workstations, maintained for the most part by graduate students. Although most universities have taken a rather laissez-faire attitude to security, as evidence of the dangers mounts, many are now adopting network programs that conceal informative files such as lists of users names, and force users to choose passwords that are hard to crack. For the long term, universities are hoping that research on computer security will discover some better way to balance security with user needs. One line of research is aiming at building a better fire wall, such as the experimental one erected by the distribution systems group of Stanford University's computer science department to protect the group's computers. Thanks to some ingenious programming, the fire wall appears virtually transparent to authorised users both inside and outside its precincts.

Source: Science, Vol. 267, 3 February 1995.

Global Warming and Human Health

Until now, concern about the potential effects of global warming – temperature increases that may occur as a consequence of industrial emissions of carbon dioxide and other "greenhouse" gases – has focused on geophysical effect such as rising sea levels and more frequent violent storms. But there are growing indications that the potential effects of global warming on human health are no less serious. Global climate models indicate the possibility of hundreds of thousands of additional deaths each year from an increase in the number of heatwaves, and tens of millions more cases of infectious diseases, most especially malaria, as mosquitoes and other pests expand their ranges. Dr. Jonathan Patz, a microbiologist working at the U.S. Environment Protection Agency, has predicted that the spread of infectious diseases will be the most important public health problem related to climate change. Even a modest global temperature increase is expected to extend the range of the vectors – the mosquitoes, flies, and snails – that transmit such diseases as malaria, schistosomiasis, filariasis, onchocerciasis, trypanosomiasis, dengue and yellow fever. Researchers have also linked short-term climate variations, including warm spells and heavy rains from El Niño to outbreaks of illness and infectious diseases, for example recent cholera outbreaks in Latin America and in Bangladesh. An outbreak of hantavirus respiratory illness in the Southwestern United States that killed 27 people in 1993 has also been indirectly linked to El Niño. The outbreak is believed to have been caused by an explosion in the deer mouse population following heavy rains from an El Niño warming that led to a jump in the animal's food supply.

One way to reduce global warming's health threat is to improve facilities for global surveillance of infectious diseases.

WHO, the World Meteorological Organizaiton, the United Nations, and other bodies are developing networks of research stations worldwide, in accordance with provisions in the 1992 climate treaty, to monitor various aspects of the environment – the atmosphere, the oceans, and terrestrial ecosystems. Increased vigilance with regard to health threats from global warming will enable scientists to anticipate where specific outbreaks are likely to occur.

Source: Science, Vol. 267, 17 February 1995.

NEUROGENIC SWITCHING

(Continued from page 3)

the central nervous system to another site. This neurogenic switching could then explain the diverse manifestations of food allergy.

Systemic anaphylaxis may be a manifestation of neurogenic switching. Cutaneous inoculation with an antigen, such as a bee sting, or gut inoculation, as in the ingestion of a food or drug, can affect multiple organ systems immediately.

Gustatory rhinitis is another phenomenon in which neurogenic switching may play a role. In this syndrome, rhinorrhea, nasal congestion, and facial sweating develop after the ingestion of spicy foods. Ingested irritants such as capsaicin, the active ingredient in chili peppers, interact with branches of the trigeminal nerve innervating the oral cavity. The efferent signal is switched to the nose and face.

Neurogenic switching may play a role in multiple chemical sensitivity syndrome, which is thought to be mediated by neurogenic inflammation. In this syndrome, exposure to respiratory irritants triggers symptoms in more that one organ system. An individual patient with chemical sensitivities often has recurrent sites of symptomatology and inflammation which reoccur with a well-defined pattern.

The multiple organ system involvement that has been so problematic in understanding chemical sensitivity also occurs in allergy. A single mechanism may underlie this switching of the site of inflammation in both allergy and chemical sensitivity. It is hypothesized that neurogenic switching is one possible mechanism by which stimulation of inflammation at one site can lead to inflammation at another. An exposure to either an allergen or chemical irritant at one site leads to a sensory nerve impulse. For allergens, mast cell degranulation leads to the release of histamine and other mediators, and histamine binds receptors on sensory nerves. For chemical irritants, receptors on peripheral nerves are directly triggered. When the impulse reaches the central nervous system, it is redirected to another peripheral location, leading to the release of substance P and other neuropeptides, producing inflammation at the second site.

An alternative hypothesis is that immunogenic switching occurs with the release of cytokines which act on distant cells. There are several differences expected between neurogenic switching and immunogenic switching. The time required for the onset of neurogenic switching depends on nerve conduction velocity, while immunogenic switching depends on circulation time and diffusion times in tissues. Neurogenic switching would directly target a particular organ in a repetitive pattern, while immunogenic switching might have a more diffuse effect. The mechanism by which the site of inflammation is shifted in both allergy and chemical sensitivity can be determined experimentally, both in controlled challenges in human subjects and experimental models. Such a program could further our understanding of these conditions while leading to improvements in diagnosis and treatment.

Source: Abridged from Environmental Health Perspectives, Vol. 103, No. 1, January 1995.

MODERN TECHNIQUES IN BIOTECHNOLOGY: BACTERIAL GENETICS AND GENE EXPRESSION

Organized by ***CHULABHORN RESEARCH INSTITUTE***
Supported by ***UNDP***

DATE: JUNE 23-30,1995
LOCATION: CHULABHORN RESEARCH INSTITUTE, LAKSI, BANGKOK

SPEAKERS

1. **Dr. Gisela Stroz,** National Institute of Health, USA
2. **Dr. Skorn Mongkolsuk,** Chulabhorn Research Institute and Mahidol University
3. **Dr. Suvit Loprasert,** Chulabhorn Research Institute
4. **Dr. Saovanee Dharmsthiti,** Mahidol University

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