'One Giant Leap'

FINAL PROGRAMME TRANSCRIPT (26/02/01)

Prof. CHRIS SHAW: (10:00:29:00) What's a nice guy like I doing in a place like this? I'm asking myself that question now. It's absolutely thundering out of the heavens here. We've been walking about a mile. We've got some nice frogs though. It's all worth it. If you work in exotic animals you've got to go find them. You can't buy them off the shelf.

NARRATOR: (10:00:46:00) And just why are these bedraggled biochemists from Northern Ireland chasing frogs in the heart of a Chinese rainforest? In fact they are harvesting small protein molecules known as peptides. All living cells produce them, frogs secrete them, science is fascinated by them, and humanity needs them.

NARR (CON'T): (10:01:26:00) The tropical rainforest: a home to more than half the world plant and animal species. Fifty years ago they covered 15% of the Earth's land surface. Today it's nearer 6% and falling. Every sixty seconds another acres are cut down for timber, cleared, or burned. A destruction of habitat that forcing many species into extinction. And when they go, they take their secrets with them…secrets that hold untold potential for medicine and human health.

SHAW: (10:02:02:00) These are the places where we find hundreds of different species of frogs. So these are the areas we concentrate upon. And basically what we have done is develop technologies where we can go into the rain forest, and without killing or destroying any individual frogs we can sample their secretions, we can bring them back out of the rain forest habitat into our high technology laboratories. There we can look for new molecules which have exciting properties, be it inhibition of cancer cells, dilation of blood vessels, or a whole variety of other biological systems. Thereby look for, in a sentient sort of way, new lead compounds for drug discovery into the new millennium.

SHAW (CON'T): (10:02:47:00) The reason we focus upon amphibians is this is an area of scientific research that was pioneered some 40 years ago by two individuals of note: Vittorio Erspamer in Italy, who concentrated on the peptides in frog secretions, and Professor John Daly from the National Institutes of Health, who was interested in the small molecules, the alkaloid molecules, as occurring in the skins of the poison arrow frogs. Unfortunately, Professor Erspamer past away, but Professor Daly is very much alive and kicking. In fact he has just returned from an expedition to Thailand where he was scaling moss covered slopes, covered in leeches, and this is the sort of thing you have to do if you want to acquire these particular specimens from nature.

NARR: (10:03:37:00) And when he's not in his Washington research lab, Professor Daly can often be found amid the extensive frog collection in nearby Baltimore.

Prof. JOHN DALY: (10:03:54:00) Well, Chris you see probably one of the biggest collections den-dra-bated frogs in the world. Their breeding has helped us for years.

SHAW: Is this what I think it is, a magic frog? What a specimen!

DALY: Looks like one of the Brazilian tree frogs, Phylomedusa. This is the one the Indians use in a hunting magic ritual. They get secretion from this frog and they burn themselves and rub it into cuts. It makes them rather sick, and then they go into a trance-like state. But the next day when they wake up they claim they're the greatest hunters in the world then.

SHAW: And they (the frogs) move so slowly so they have to have a really very powerful cocktail of toxins against their predators.

DALY: Something to ward off predators which would find this an easy prey otherwise. Beautiful frog…beautiful frog.

SHAW: A spectacular species.

DALY: These I've heard calling in the forest many times, and I look up and I say, okay 60-feet up in the tree there's a male of these Phylomedusa calling. Well, that does me a lot of good (laughs). The few I've collected in the wilds are probably just been clumsy ones that have fallen out of the tree…

DALY (Con't): (10:05:01:00) Epibetadine is probably our most exciting finding in the 40 years of working on these poison frogs. It was part of an expedition to Ecuador. We were looking to see what type of compounds were in the poison frogs of Ecuador. Fortunately when I got back I took the extract from this one frog and injected it into a mouse, and the mouse immediately arched its tail up over its back, and I recognized that this as an old test for morphine-type compounds…the 'Straub tail test.' We collected frogs, we isolated the compounds, but we did not get enough to determine the structure, and we had to wait twenty years until the scientific instruments became sensitive enough to determine what it is. In pursuing it further we discovered a morphine-type compound, but it was a compound with much more potent activity as a pain killer than morphine. For people who suffer from chronic pain, you ask them whether the rainforest is important and they'll say yes.

JACK COVER: (10:06:09:00) In our rainforest exhibit here at the National Aquarium in Baltimore we do display some animals that are critically endangered at this point. One example is the Golden Lion Tamarant, which unfortunately lives a little bit too close to Rio Di Janiero in Brazil. The area where it lives is highly populated, and about 90% of rainforest home has been destroyed.

NARR: (10:06:32:00) But there is a twist in the tale for this handsome little monkey. It's obvious popular appeal has produced action. Not only to protect its habitat, but to extend that protection to neighboring areas.

COVER (Con't): (10:06:44:00) Unfortunately, there is an example given with rainforest destruction that's like a library burning down before we've read all the books in the library. That is happening all the time. Because of the destruction we really have two lists going: the new species being discovered and the ones that we're losing to extinction.

DALY: (10:07:05:00) I think many of the compounds that we and the compounds that Chris Shaw is isolating really show why the bio-diversity is so important. What Chris Shaw is looked at is peptides. And he's found that all the frogs in the world are rich sources of peptides, novel peptides, interesting compounds, some of which are found nowhere else in nature, and certainly will open up a whole new era of biological research.

SHAW: (10:07:50:00) There are over 4,000 species of frogs, and here in China there are several hundred species, and several hundred more waiting to be discovered. So we're here to collect the secretions from the frogs, take them back to the laboratory and determine what types of molecules a present. Do they have biological affects…?

SHAW (Con't): (10:08:11:00) I think the frogs were going to be eaten anyhow, you know? I think people in the West have got to remember we don't have any supermarkets here. We're 400 miles inland, in Upper Wuiysan Province, and people here have to eat what is available. And people here have to eat what is available and people for centuries have been eating these frogs, which are a very good source of protein.These were frogs that were destined for the pot anyhow. But it also conforms with another golden rule in biology and that is that sooner or later all biologists who work on an animal end up eating it.

LI LONG, Research Student: (10:08:42:00) A farmer who live here and he catch the snakes and sell to this kitchen. The snake in Chinese it means 'five step snake'. It means if you was battened by this snake after you walk only five steps you will die.

ROB ROBINSON, Research Student: (10:09:03:00) There's a member of our team works with snakes, so I'm pretty sure that he would be keen to get his hands on the venom. But you're not going to get me milking these guys.

NARR: (10:09:12:00) In China you never know what you might be eating, or who might join you.

ROBINSON (Con't): (10:09:23:00) It's perfect frog territory. Absolutely fantastic. You've got a plentiful supply of water. You've got a lush vegetation. The temperature is just perfect for these animals. This is, this is absolutely fantastic…

ROBINSON (Con't): (10:09:55:00) We're using the local talent here…the guy is phenomenal…he seems to just have a nose for these things…he's in there finding frogs that I can't even see…

SHAW: (10:10:32:00) …Could be another species of (?) frog…maybe even a new species…

NARR: (10:11:12:00) The peptides being isolated for intensive study by Chris's team are natural but complex proteins, comprising anything from two to 40 or more amino acids. And a powerful weapon in frogs' defenses against predators.

Prof. PING FAN RAO: (10:11:27:00) Chris is definitely a top guy in this field. We have all those frogs running around but we didn't put focus on those frogs before he came. That's a really terrible waste of a good resource. I have a group of bright people

working in the lab, but they don't have great opportunity to learn, to get better training. Through this joint project I can see that I would turn my group into one of the major peptide research center in China.

ROBINSON: (10:11:59:00) This, for me, is one of the pleasures of the job, because we get to put the animal back into its environment again, which no permanent harm has been done to the animal, and he's off back into his natural environment. We've got the secretion and they've got their freedom…

SHAW: (10:12:16:00) The Chinese Giant Salamander may hold the key to unlock the process of aging of human cells. This creature was probably around long before the dinosaurs. And a very, very interesting group because they seem to live for goodness knows how many years? This one was probably about a third grown, and maybe 12 to 20 years old. So these are very long lived animals and they may hold some of some the secrets of the aging process themselves that we can unravel for aging research.

SHAW (Con't): (10:12:49:00) It's necessary for the scientist to do just as we have done in the past week – go out into the field and actually collect specimens. And of course this is really taken biology into the real world, not just ordering things out of chemical catalogs but going out across the world, here in the Far East, to actually collect the specimens, remove their secretions, and then synthesize these chemicals without danger to the animals…

SHAW (Con't) (10:13:24:00) Previous studies on frog skin peptides necessitated killing the frogs, removing their skins, then chemically extracting this. But the development of new technology which facilitates a technique which involves simple electrical stimulation of the frog, which is very gentle…equivalent to the current that's used in acupuncture…

ROBINSON: (10:13:50:00) This is our tree frog, it's a little Litorea Caerulea…White's tree frog. It's a little Australian tree frog. The first thing that I'm doing is conditioning the skin with a little water. This makes it easier for her to secrete whenever we put the electrodes onto the skin. These are two just ordinary electrodes, and we're just applying a miniscule electric current here to the skin. And what we're doing is we're just causing the muscle under the skin to contract. Once we've done that we then just wash the secretion off the frog into beaker. That's it. You can see that our frog completely un-phased by that. It's quite happy. What we've got here is a fairly complex cocktail of chemicals containing peptides, proteins, biogenic amines and various other alkaloid compounds…

SHAW: (10:14:58:00) The first stage is actually reducing the volume of the venom we take. Because we wash it off with distilled water we have a reasonably large volume. So we use a technique called lyophilization, or freeze-drying, which effectively keeps the molecules at a very low temperature so there's no degradation. We remove the water from them under vacuum so we end up with a white powder. That is then reconstituted in small amounts and subjected to fractionation using a high technology system whereby we can resolve each component of the venom.

DR. STEPHEN McCLEAN, Research Officer: (10:15:38:00) Each frog venom contains a very complex mixture of chemical compounds. And the first stage in our analysis is to separate all those components into the various constituent parts. So the first thing we do is take some of the frog venom, we dissolve it in some water with acid, and then we inject it onto our chromatography system. The chromatography system separates the components: first of all the small molecules followed by medium sized compounds, such as peptides and alkaloids, and finally molecular weight compounds such as large peptides and proteins (elude-plast)… Approximately 90% of the liquid is collected and used for further analysis, while roughly 10% goes into our mass spectrometer where achieve date regarding the size of these compounds.

DR. DAVID ORR, Research Officer: (10:16:43:00) We spot our samples onto a hundred well plate, let them dry with a matrix. Then we put the sample into the machine and we fire a laser at the spot that we're interested in. The sample then goes up the time-of-flight tube and is detected at the top and this is what we see on the screen…and we can identify the mass of the peptide we're interested in…

SHAW: (10:17:16:00) This is the third stage in the procedure, where we actually sequence the peptide. The peptide is immobilized here, these reagents are then delivered, and it's broken down amino acid by amino acid. The amino acid is then…

NARR: (10:17:29:00) Links with the University of Fu Zhou are already bearing fruit. Li Long and Abwa, last seen wrangling frogs in China are now PhD students with Chris, and rapidly coming to terms with his high tech laboratory.

SHAW: (10:17:51:00) We can test for a whole range of different biological activities. And one of our frogs, Pachymedusa, a frog from Central America, from Mexico in fact, we screened this frog quite recently and we found that it actually contained at least 14 different vasodilator peptides. We then subsequently went through these one at a time, we determined their structure and indeed the first one of these that we structurally characterized turned out to be a new class of frog skin peptide.

NARR: (10:18:24:00) In this research the Coleraine team are working with the Radiation Biology Unit at the University's Jordanstown campus near Belfast. To test the effect a small section of artery from a rat's tail. It's then placed in a heater block to maintain normal body temperature and bathed in a nutrient solution, which mimics blood. A powerful constricting agent is then added, which narrows the artery and reduces blood flow. 10 minutes later, when maximum pressure is reached in the artery, a solution containing the peptide produced by the frog Pachymedusa is substituted for the constricting agent. Just 30 minutes later there are significant results.

MARTIN O'ROURKE, Research Student: (10:19:26:00) At the moment we're seeing approximately 50% reduction in blood pressure in this system. This is a real breakthrough. Things like this have never been seen before. The vaso-activity that we're getting at such low concentrations could prove to be very, very vital in developing therapeutic treatments and also in managing regimes. We can now look at delivering drugs to tumors more effectively at lower concentrations of drugs. We can also look at

giving it to hyper-tensive patients to lower their blood pressure, again at very, very low doses.

SHAW: (10:20:02:00) Pachymedusa is a frog that produces copious amounts of venom. If you look at venom from other creatures you will see that they often contain molecules with anticoagulant properties, because the introduction of venom into the circulation will often cause blood to clot. So they contain molecules that prevent that so the venom can spread.

NARR: (10:20:25:00) Hematologist Dr. Billy Gilmore provides a simple demonstration under laboratory conditions. First he takes a sample of normal blood plasma and adds a powerful blood-clotting agent. With the sample held at normal body temperature, clotting occurs within 15 seconds. However, when he adds the same clotting agent to a sample which contains the anticoagulant peptide provided by Pachymedusa, there is no clotting. The clock just ticks on and on. Pachymedusa's anticoagulant properties have great potential for the prevention and treatment of deep vein thrombosis and heart disease…two of today's major killers.

NARR (Con't): (10:21:34:00) One of the first peptides discovered by the team came from Kassina Maculata from West Africa. Chris was astonished to find its protein was virtually identical to one found in the nervous system of some insects, a protein known to cause severe hyperactivity in the muscles, ending in total paralysis.

SHAW: (10:21:57:00) The reason the frogs produce this compound as we found out later was that their major predators in the African rainforest are the giant water insects. And what I mean by that are diving beetles that are maybe 15cms long and capable of taking out half a cubic cm of flesh from your big toe if you happen to encounter one while wading through the water. So it's astonishing that even in terms of defending themselves against predators that are invertebrates that the frogs, through the course of evolution have come up defensive chemicals in their skin. And of course such chemicals are of enormous interest to the biotechnology industry, because cloning peptides such as this into either food crops or into plants such as cotton could effectively make that plant resistant to insect attack. Which means you don't have to spray insecticides randomly into the environment.

SHAW (Con't): (10:22:51:00) Litorea Caerulea and allied frogs of that particular family which occur in Australia contain a vast number of peptides that potent antibiotic activity. And very early on in the study of these frogs we determined that their activity was not just directed against ordinary or common garden organisms, but they were equally effective at killing some multiple drug-resistant human pathogens. Those that cause human disease and that effectively cannot be treated by conventional antibiotics.

SUSAN FARRAGHER, Research Student: (10:23:22:00) These compounds work in a completely new and different way to traditional antibiotics. This is very important at the moment because of the ever increasing number of resistant organisms that emerging worldwide. And our compounds, they work in a way that microbes cannot become resistant to them.

SHAW: (10:23:46:00) One of the reasons for this is the way in which the antibiotic molecules work. They imbed themselves in the membrane of the bacterium and they form pores, effectively they burst the cell.

NARR: (10:24:00:00) For this North American frog, Rana Pipiens, the giant leap is toward the treatment of cancers. Molecules, secreted from its skin, have proved to be from a similar source to the so-called messenger molecule produced in the human body, which are known to either stimulate or discourage the growth of tumors.

SHAW: (10:24:18:00) When we screened a frog called Rana Pipiens we found a peptide which had profound effects on inhibiting the growth of tumor cells from a wide range of different tumors. We also determined it had receptor for this peptide, a binding protein on the membrane of the tumor cell. This peptide also inhibits the differentiation of bone marrow cells into white blood cells. So such a molecule may have implications in for instance the treatment of leukemia, the arresting of the damage to the bone marrow during chemotherapy, and wide range of other applications per chance in the treatment of cancer.

NARR: (10:24:52:00) And the success stories continue. Each new peptide that is isolated and analyzed presents an exciting new discovery to the University of Ulster team. And each has the potential to be one more giant leap for medical science.

SHAW: (10:25:08:00) Traditionally the shaman, or the medicine man in native tribes passed this type of medicinal information down to their sons, to their grandsons. Now in our high technology generation the same thing actually happens. One young scientist obtains inspiration from an older scientist and carries that through to his students, and passes that on through generation to generation. And if one goes back to the concept of the rainforest one looks at the rainforest, at the animals, at the plants, at the beautiful flowers and one thinks as a human this is a beautiful place. But one must remember that the rainforest is a battleground, that for millions of years each organism that exists in the rainforest has been vying with every other organism for survival. It's basically a case of biological warfare. But what I think is very, very important is that we as human society use that biological weaponry that has been evolved over millions of years, and we use that to put that against the things that are a real threat to humankind: cancer, heart disease, neuro-degenerate diseases. I believe the cures for these exist in the rainforest, in the molecules that have evolved over millions of years in organisms. So basically what I'm saying is that I believe we can put those weapons to use for the good humankind in the ultimate defeat of these diseases, which so far have remained intractable.

END TRANSCRIPT.

‘One Giant Leap’

Narrator	Lesley Black
Expedition Footage	Brian Black
Lighting Cameramen	Richard Blakslee Michael Quinn
Sound	Haven McKinney Ronan Hill
Gaffer/Spark	Doug Ray Kevin McCarthy
Frog Wrangler	Zachary Zamora
Music Performed by	Davey Spillane Karen Matheson
Archive Footage	World Images WWF
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VT Editor	Gary Dalton
Write/Producer	Lesley Black
Director	Daniel Hoffman
Series Editor	Ron Blythe

‘One Giant Leap’

1) Copyright Music

“Celtic Themes” BRR44 Bruton Music Ltd
165 – 167 High Road
Willesden
London
NW10 2 SG

Composers: Mike Trim/Buddy Blyth
Performed by: Karen Matheson (vocals) & Davy Spillane (pipes/flute)

Tk9, “Eype 1” – Duration 1x45”

Tk19, “Celtic Fun Part1” – Duration 1x20”

Tk22, “Rythms of the Moon” – Durations 1x25”, 1x30”, 1x30”, 1x52”

Tk24, “Jenny’s Lament” – Durations 1x30”, 1x28”

2) Non Copyright Music

AVP Music Library
The Studio
239 Worcester Road
Malvern Link
Worcester
WR14 1SY

(PRS Number 161674468)

AVP 003	Tk1	“Shak to the System” – Duration 0:11
AVP 005	Tk11	“Silk Road” – Duration 0:11
AVP 008	Tk14	“Lotus Flower” – Duration 1:38
AVP 008	TK 26	“Computer Virus” – Duration 0:26