TREATMENT

Limb salvage, which is the aim of surgery, has produced some interesting features. Of the two patients with upper limb involvement, one was discharged from hospital with an arm intact and will full function. The other patient died within 8 hours of admission to hospital. Of the 14 patients with lower limbs involved, 4 remained intact, but only one retained full function, the others having varying degrees of altered function. There were 10 amputations (or further amputations) of which 8 were carried out for gas gangrene. The remaining 2 were late amputations for long-term developments - chronic osteomyelitis and chronic limb deformity. It should be of special note that no disarticulation of any limb was performed. This used to be considered the operation of choice for high Clostridial limb infection. However, the emphasis today is on limb salvage and retaining as much tissue, muscular and bony, as possible (Hoffman et al. 1971). In case 12, a previous above-knee amputation after trauma developed gas gangrene spreading up to the abdomen and required further amputation. Even in this case it was considered expedient to perform a subtrochanteric amputation rather than hip disarticulation.

In all cases, as seen from Table 1, hyperbaric oxygen was administered, ranging from a single session to a lengthy 18 sessions, with an average of approximately 6 per patient (excluding the single treatment sessions in the case of patients who died). Each session lasted two to two and a half hours and was conducted at 3 ATA, or the pressure equivalent of 66 feet of sea water. Usually 3 sessions were administered in the first 24 hours with a further 2 sessions each subsequent 24 hours, dependent on clinically evident improvement in the patient's condition. No serious complications from the use of hyperbaric oxygen at 3 ATA occurred. There were no convulsions in any patients during any of the 104 sessions, though on several occasions early warning signs - increased restlessness and anxiety, nausea, pallor, profuse sweating and a rise in blood pressure - were noted, especially in the severely toxic patients. Aural barotrauma from an inability to equalize pressure on the tympanic membrane occurred in 2 patients. Both suffered middle ear haemorrhage with subsequent hearing loss. Their hearing improved after a few weeks. No other form of barotrauma was noted.

Penicillin was the antibiotic used in every case of Clostridial gas gangrene in this series. The policy as Prince Henry Hospital is to use large doses of benzyl penicillin administered intravenously every hour. No patient received less than 600mg hourly, with the exception of the patients in Cases 6 and 7, who being in renal failure, received 600mg every 4 hours. The upper level of penicillin dosage has been 1800mg hourly, given to 4 patients with the most severe and rapidly spreading gangrene. This dose was reduced to 600mg hourly after 3 days in the case of 3 of these patients, but one (Case 12) continued on this regime for two weeks, and developed the comparatively uncommon condition of penicillin-induced haemolytic anaemia. Such high doses reported initially to be sensitive to penicillin. They were both challenged with purified penicillin (purapen) and found not to have sensitivity. They then were given full intravenously administered therapeutic dosages of penicillin. Gas gangrene antitoxin is not used prophylactically or therapeutically.

Of the 13 cases of trauma, only 5 patients had received penicillin prophylactically at the time of injury. The doses ranged from 300mg intramuscularly every 4 hours to 600mg given every 6 hours. In only 2 was an immediate high dose administered intravenously (both 6gm). It is obvious that more thought must be given to improved penicillin prophylaxis in cases of trauma.

CONCLUSION

Of the 27 patients referred to the Prince Henry Hospital with a diagnosis of gas gangrene, the condition of 20 was severe enough to warrant the triple treatment of hyperbaric oxygen, surgical debridement or selective amputation, and high doses of penicillin. That these cases occurred in the space of 21 months in New South Wales alone has suggested an abnormally high incidence in this State, but the management of this severe disease has proved reasonably satisfactory, with a mortality rate well in line with the best of overseas experience.

RECENT RESEARCH IN MARINE PHARMACOLOGY

by John Fox

The Americans with their usual enthusiasm for statistics recently analysed 1.05 billion prescriptions which were dispensed through higher community pharmacies in the USA. Of these 50% of the medication prescribed was of a synthetic nature, 25% came from higher flowering plants, 12% from microbes, 6% from animals and 7% from mineral sources. However, of these non-synthetic preparations only a fraction, perhaps less than 1%, originated in the sea. This is surprising when one considers that 71% of the earth's surface is underwater and four fifths of the 500,000 species of animals live in or near the sea. If one looks at it purely from a statistical point of view there must be a great potential to find pharmacologically active substances in the marine environment.

With this in mind I had a look at the recent research being done in this field. The first thing you notice is that it is being carried out by a very small number of people, small not only in numbers but also in their financial backing - often individuals or one or two people working in aquariums and universities and perhaps occasionally working for a drug firm. This situation is about to change with the development by Roche of its $4 million Institute of Pharmacology at Dee Why.

The drug firms generally are not very interested in this field, because, while many of them appreciate the tremendous potential of a new find, and obviously the sea can yield many of them, the problem arises that it is difficult to get large quantities of pure active material from a marine source. For example, the recent research carried out by Peter Williams to isolate Macula Toxin from the Blue Ringed Octopus at the Macquarie University is a case in point. Williams followed on work done by Howden - the whole work has taken approximately thirteen years. He himself spent at least two years in isolating the toxin. To get sufficient material to work with he used 400 octopi to make something like 200 mgm of crystalline material, half of which is sodium chloride, so you might say four hundred blue ringed octopus produce 100 mgm of pure macula toxin. One can gauge the potency of the toxin particularly when it is realised the blue ringed octopus bite is like a parrot's, that he has a very small beak and that the toxin is not injected by merely runs into the wound as part of the saliva. Therefore it must be lethal to adult humans in quantities of the order of less than 0.25mgm without allowing for wastage, etc. In fact tests with the blue ringed octopus in tanks have revealed that, when the creature has not been starved, live crabs dropped into the tank are not bitten by the octopus. It merely releases some of its toxin near the crab and waits for paralysis to take place then devours its prey at leisure. However, when the octopus is very hungry it will attack the dorsal surface of the crab, biting through the shell and clinging to the creature until death, when it efficiently removes the shell and consumers the flesh.

However, to return to the main topic, this is hardly an encouragement to any of the drug companies to rush in and start to analyse the various possible therapeutic values of macula toxin, although it perhaps has an eventual use as an anaesthetic or as a tool in the better understanding of nerve activity in excitable membranes. Nevertheless, one well known manufacturer of anaesthetics is already working on this.

Usually a drug company, when they come to do the vase research necessary to find the therapeutic activities of a new substance requires tremendous quantities of the material in a pure crystalline state. One can be a little sympathetic to the drug companies when one looks at the situation with cephalosporin. The original work was started back in 1948 by Professor Brotzu, University of Cagliari, Italy, but it was not until 1964 that a product had been sufficiently developed to market. During that time as many as 200 researchers were working on the substance at any one time, particularly in the latter years, and quantities of the raw material were required in kilograms. It will be remembered that Professor Brotzu found his original spores in the sewerage outlet off the coast of Sardinia. There may be an important link here with recent research into the sea sponges (by Clive Wilkinson of University of Queensland and Dr Ross Nigrelli of Osborne Marine Laboratories in New York) which are found to possess antibiotic properties in 50% of all sponges so far tested. It has been further noticed that sponges tend to increase in number in areas near sewerage outlets - Roche has made this one of their first areas of research at their new Institute. So far the first named antibiotic 'Ectyonin' has been isolated from the sponge Microciona Prolifera (reference Marine Biotoxins, Dr R Endean). From a West Indian Sponge a unique form of Nucleic Acid has been isolated by Cohen which is effective against certain viral infections and Leukemias in man and a synthetic derivative is capable of inhibiting the growth of Sarcoma 180, Ehrlich Carcinoma and L-1210 Leukemia in mice.

I think we are all familiar with the number of substances which are in current use today which have a marine origin, such things as protamine which is obtained from the sperm and testes of certain fish such as salmon. Tetrodotoxin, from puffer fish, has been in use in Japanese folk medicine since the days of the Saurai for the treatment of a wide variety of disorders from myalgia, asthma, neuralgia, syphillis and arthritis but has recently been re-examined, and is in use in Japan today as a palliative in terminal cancer being 160,000 times more effective than cocaine. Its obvious drawback being its toxicity (10,000 times that of Sodium Cyanide).

Research in the marine field is carried out in much the same way as research on land. Observe then investigate. An interesting observation was that the Antarctic penguin has an absolutely sterile gut. This fact was followed up and it was found that this was due to the fact that they eat certain crustacea (Krill) and these in turn feed on Blue Green algae which in turn contain a powerful marine antibiotic, Acrylic Acid - an active and effective antibiotic against pathogenic bacteria and yeasts.

It has been found that certain sea cucumbers when molested eject material called Cuvierian tubules which are highly toxic to almost all sea creatures and which are effective in a dilution of one in one hundred million. Surprisingly, the same substances appear to have anti-tumor activities and when tested against Sarcoma 180 and Krobe 2 tumors in mice cause regression. Certain extracts of this toxin are found to have a digitalis like action and it is thought that perhaps this might be more effective than digitalis in the correct dosage. The toxin also ha haemolytic properties blocking nerve condition and is useful in controlling spastic conditions in humans following brain or spinal damage.

Certain anti-cancer characteristics are exhibited by the clam and it is interesting to note that these anti-cancer characteristics vary with the time the clam is harvested. If it is harvested during the summer the anti-tumor characteristics are much higher and if the clam is allowed to develop in polluted water it has no anti-cancer characteristics. If it is harvested during the winter the anti-tumor characteristics are very very low. Clams yielding the greatest amount of anti-tumor characteristics are those which have been allowed to winter in especially heated clean salt water. Another substance to be isolated from clams is the herapin like group of mactins.

First interest in the clam's anti-viral characteristics were commenced by a scientist - who possibly did not care for them as a food when he made a pathological examination of tinned clams intended for human consumption.

A potential drug which may be obtained from the Toad Fish is contained in the venom of four poisonous spines on its back and gill covers and has the characteristic of increasing the metabolism of sugar in much the same way as insulin does. Certain fractions of the stone fish venom are found to be very hypotensive as are some of the fractions from the macula toxin of the blue ringed octopus. One researcher claims that liver lipids obtained from the shark enhance the body's resistance to cancer and the sting ray produces a potent cardiac depressant. Of course one of the substances which is undergoing a tremendous amount of research at the moment is prostaglandin. The problem has always been, and still is for that matter, the tremendous difficulty in producing any large quantities. These have come from mammal sources until recently when it was found that certain kinds of sea whip or sea fan produce something which is very similar to prostaglandin and only requires a small amount of chemical treatment to yield the active varieties of prostaglandin.

From the Star Fish, which is a relative of the prickly spined Sea Urchin, comes an excretion which has proved valuable as a muscle stimulant as well as an effective contraceptive.

Perhaps an area of somewhat bizarre research covers such things as the investigation into the electric eel which produces a discharge of some 350/650 volts over a distance of 20 feet. It is thought that if some sort of biological battery could be developed along these lines for man it would be of great value in space travel.

Another unusual item of research is that being done on barnacle cement. It is a liquid which hardens in some 15 mins and has a strength of 22lbs per square inch and would obviate the need for dentists to 'key-in' fillings if it could be developed to the necessary extent.

The ability of certain star fish and amphibians to regenerate limbs is being researched by Dr Robert Baker - Veterans Hospital, Syracus, USA. Dr Baker, through study of the Salamander has found that regeneration seems to depend on electric stimulation at the site of loss which causes cells to turn from their normal formations and form blastemas (the protoplasmic building blocks necessary for new growth). he theorises that while humans use a similar electrical process to heal broken bones (the broken ends causing an electric field with different polarity at either end of the break) evolution has caused mammals to have most of their electrical activity in the brain and it is therefore not available to regenerate limbs. (Current at the amputation site in a mammal id 30 times less than in a similar site on a starfish or salamander). Using electrical stimulation Dr Baker has been able to cause the regeneration of an entire humerus from the site of an amputated leg of a mouse.

One field of research I have not touched on is the use of sea creatures as a tool in research itself, eg. the use of sea urchins, because of their relatively simple life cycle, to test the teratological effects of drugs and give the results in a matter of days rather than months or years.

The Hag fish is being used for experiments in skin grafting because it is devoid of a thymus gland and therefore is thought to have no immune reaction to grafting. However, skin grafts are rejected after a period of 70 days (compared with 14 days for mice) and secondary

grafts are rejected in 30 days, indicating an immunological memory. Hagfish only produce one type of serum antibody which is through to be a basic evolutionary 'building block', and which should be useful in the understanding of the evolution of the immune response.

As can be seen a great deal of the research being done at present will take many more years before fruition and possibly much of it will amount to nothing, but undoubtedly many breakthroughs will be made in this virtually untapped field of potential in the years to come.

CLINICAL CASE REPORT

HISTORY

SUNDAY 15TH APRIL (Sydney time) 1973

Dive 1.30pm The patient (a 29 year old Nauruan Islander) underwent a dive to approx. 250 ft (bottom depth) for 20 min. Reason for the dive was treating another diver for 'pain only' bends. No previous dives on Sunday. Dive to ?200 ft for ?10 minutes preceding day (details of depths and times difficult to ascertain). Shortly after leaving bottom the patient ran out of gas and surfaced immediately (? using emergency supply).

10 minutes after surfacing he noticed dizziness and vertigo (self rotating in environment) and inability to walk straight. There was also some 'numbness' of both lower legs.

One hour late rthe patient noted weakness of the right leg. This progressed over the next hour to a total paralysis of the right leg and a marked weakness of the left leg. He was then admitted to Nauru General Hospital.

Five hours after the dive he was noted to have severe abdominal pain, vomiting, paralysis of right leg, paresis of left leg with a total sensory loss of mid thigh level right leg and knee level left leg. He was given 100% O_2 by mask during which time the vertigo apparently settled and the leg anaesthesia largely resolved.

Arrangements were then made to transfer him to HMAS Penguin by Air Nauru (Fokker Fellowship).

MONDAY 16TH APRIL

4.00am On arrival at the School of Underwater Medicine at HMAS Penguin, he was noted to be conscious but drowsy and weak. Pulse rate: 100/min. BP 130/100. HS normal, chest clear. Abdomen soft but tender, non-distended and no bowel sounds noted. Bi-lateral grade I aural barotrauma. In-dwelling bladder catheter in situ. IV infusion into (R) leg had become blocked.

Positive neurological findings were :-

Right beating nystagmus - exaggerated on right lateral gaze, abolished on left lateral gaze.
Mild left upper limb inco-ordination.
Equal power, tone and reflexes in both upper limbs, but weak.
Complete paralysis of right lower limb with marked weakness of all muscle groups of left lower limb (could just flex knee and ankle).
Lower limb tone was equal, perhaps reduced, but reflexes were increased on the right side of ankle clonus. Plantar responses were flexor.
Sensation. Light touch and pin prick sensation intact but equivocal results were obtained with proprioception and two-point discrimination.

A diagnosis of Spinal Decompression Sickness (involving lumbar segments L2. L3-L4 region) was made. An IV infusion was recommenced and he was given Lasix 20mg and Decadron 8mg in infusion.

5.45 am He was placed in the recompression chamber and was given Stemetil 25mg IMI for nausea. At this stage the nystagmus was no longer present. After 10 minutes at 30 ft on 100% O_2 no change was noted except that lower limb reflexes were absent. No further change after 10 minutes at 60 ft.

He was changed to 40% O_2 and compressed to 120ft for 10 minutes - no change. After 10 minutes at 165ft on 40% O_2 the reflexes were noted to be brisk but there were no other changes. He was decompressed to 60ft at 10 ft/min and then decompressed according to Table 6B (RAN) - the long O_2 table.

7.00 am A Rheomacrodex infusion was commenced (500ml over 5 hours). No improvement was noted until 1.30pm when slight contraction of the right quadriceps was noted.

2.00 pm The chamber reached the surface. On examination, the patient was able to elevate his right knee 4-5" off the bed. Power had increased in the left leg. Reflexes were brisk with slight right ankle clonus. Abdominal tenderness was less. 100% O_2 by mask was continued 1 hour on, 15 minutes off until 8.00pm.

TUESDAY 17TH APRIL

An attempt at spontaneous voiding overnight was unsuccessful and he had to be re-catheterised. There was no change in his neurological status. He was still on IV fluids and Decadron.

10.00 am He was given hyperbaric O_2 for 60 minutes at 60ft with an ascent of 3 min/ft. Following this session there was a marked increase in the right quadriceps contraction and some slight hamstring contraction noted.

2.00 pm A further episode of OHP was given. Following this a further improvement in power in te right quadriceps and hamstrings was noted and for the first time, weak plantar flexion at the ankle. Power in the left leg had also improved. More detailed sensory testing