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SKIN INFECTIONS IN OCCUPATIONAL SATURATION DIVERS IN THE NORTH SEA AND THE IMPACT OF THE ENVIRONMENT

Trondheim, Juni 2003.

CONTENT

LIST OF PUBLICATIONS

Paper I — Ahlen C, Mandal LH, Iversen OJ. Identification of infectious Pseudomonas aeruginosa strains in an occupational saturation diving environment. Occup Environ Med. 1998 Jul;55(7):480-484.

Paper II — Ahlen C, Mandal LH, Johannessen LN, Iversen OJ. Survival of infectious Pseudomonas aeruginosa genotypes in occupational saturation diving environment and the significance of these genotypes for recurrent skin infections.Am J Ind Med. 2000 May;37(5):493-500.

Paper III — Ahlen C, Mandal LH, Iversen OJ. The impact of environmental Pseudomonas aeruginosa genotypes on skin infections in occupational saturation diving systems.Scand J Infect Dis. 2001;33(6):413-419.

Paper IV — Ahlen C, Mandal LH, Iversen OJ. An In-field Demonstration of the True Relationship between Skin Infections and their Sources in Occupational Diving Systems in the North Sea. Ann Occup Hyg. 2003 Apr; 47(3):227-233.

Paper V — Ahlen C, Iversen OJ, Risberg J, Volden G, Aarset H. Diver's hand: a skin disorder common in occupational saturation diving. Occup Environ Med. 1998 Feb; 55(2):141-143.

Appendix — Ahlén C., Mandal LH, Iversen Oj and Aarseth H. *Kytococcus sedentarius* – a possible contributor to "Diver's hand"?

ACKNOWLEDGEMENTS

The present work has been carried out at SINTEF (The foundation for Scientific and Industrial Research at the Norwegian University of Science and Technology, Trondheim) in close co-operation with St. Olavs Hospital, Department of Microbiology, Trondheim. I am very grateful to my former manager at SINTEF, Arvid Påsche, who together with Alf Brubakk introduced me into this very unique and interesting field and to Paul Hellandsvik, Randi E. Reinertsen and Tonje Hamar, who supported me through the final steps towards this summing up. I'm also indebted to professor Johan Meland at Dept. of Microbiology for the generosity regarding facilities, equipment and valuable discussions.

The annual financial support obtained since 1988 from the Norwegian oil companies Statoil, Norsk Hydro, Saga Petroleum and Esso Norge and the Norwegian Petroleum Directorate, canalised through the long-term research programmes of diving medicine and technology (FUDT, OMEGA and FOU) has been the key factor for a systematic work in this special field of interest. I do express my gratitude to those involved in this support and in particular to Cato Hordnes and Einar W. Svendsen. I also wish to express my gratitude to the diving companies Stoltoffshore (earlier Stolt Nielsen Seaway /Stolt Comex), Subsea7 (earlier Rockwater/Halliburton) and Coflexip Stena Offshore and the personnel on board the operative diving vessels for their support in terms of man-hours and engagement and last but not least, to all the brave divers who's never-failing enthusiasm has been very encouraging.

Through the years, it has been a great pleasure to collaborate with so many skilled and generous professionals both within hyperbaric-related work (Nui and Haukeland

Hospital, Bergen) and the impressive medical and technological environment based upon St Olavs hospital, NTNU and SINTEF - I'm deeply indebted to all of you. In particular, I wish to express my sincerest gratitude to:

- Professor Ole Jan Iversen, my collaborator from the very beginning of my work on extreme environments and my supervisor during the entire period of the thesis work. I do admire his support whether visible or invisible and I'm deeply indebted for having got the opportunity to learn from the logic discussions, which often ends in new approaches.
- Lise H Mandal, my skilled lab collaborator through the past ten years and thus indispensable.
- Professor Are Dalen for the many fruitful discussions and open-minded view to "new" microbiological characteristics emerging in the material from this extreme environment.
- Ingrid Leinan, Augusta Kvam and Grethe Lysholm Iversen for making the *Pseudomonas aeruginosa* biobank possible.
- Hilde Lysvand, for innumerable small "pilots".
- Odd Gunnar Brakstad for inspiring scientific discussions on research ideas.

I also wish to express my sincere thanks to:

- The whole personnel at Dept. of Microbiology for always being inclusive, obliging and helpful, and in particular those who have handled the North Sea samplings.
- Erik Kindseth, Finn Bakke Olsen and Jon Steinar Kvaale for "ad hoc" help with photos and graphics whenever.

- All colleagues and friends for just being there and in particular Ingve & Siri, standby through 20 years.

Finally, the most important of all, Carl Henrik and Therese, my beloved family who always are awake for a midnight snack and gossip.

ABBREVIATIONS

ABF Antibacterial factor

COPD chronic obstructive pulmonary disease

CDC Centers for Disease Control and Prevention

GAS Group A streptococci

DH "Diver's Hand"

IATS International Antigenic Typing System

MRSA Methicillin resistant *Staphylococcus aureus*

Msw meters of seawater

NPD Norwegian Petroleum Directorate

PCR Polymerase Chain Reaction

PFGE Pulsed Field Gel Electrophoresis

RO Reverse Osmosis

ROV Remotely Operated Vehicle

INTRODUCTION

The technical framework of saturation diving makes it a much specialised occupation and the confined environment is in itself biologically and physiologically extreme. Additional factors, such as the environmental role of microbial growth and survival as well as chemical pollution of seawater, make this niche unique with respect to human exposure. Since the start of saturation diving on the Norwegian offshore sector, hundreds of thousands of man-hours have been spent within such unique and highly extreme occupational working systems (*NPD dive database*). Serious attempts to establish unmanned deep water interventions by Remotely Operated Vehicle (ROV's) as a first choice were made at the beginning of the 90's, but since then, manned intervention, i.e. deep diving, has once again become the method of choice for maintenance work in medium-depth waters (30 - 180 msw).

This thesis focuses on the potential role of the environment in skin infections caused by *Pseudomonas aeruginosa* in North Sea deep divers.

1. OCCUPATIONAL SATURATION DIVING

In the opening chapter, I provide a brief introduction to a saturation diver's unique and extreme working and living environment, as this is not common knowledge but of vital importance for understanding of this problem area.

1.1 History and technical description

Oil exploration in the North Sea began on the UK continental shelf in the late 50s and on the Norwegian continental shelf in the late 60's. The first Norwegian oil field explored for production was the Ekofisk field, in which oil was found in 1969 at 3000 m below sea level, and where production started in 1971. More than 30 years on, the oil property is worth about NOK 2100 billions, or about NOK 100 billion a year in income for the country.

Oil exploration in deep, dark and cold seawater demands highly advanced technical systems, many of which include manned underwater intervention, i.e. deep divers capable of installing and maintaining the structures. Engineering techniques have improved methods of working at depth in the open sea, and the technique of saturation diving, developed in the US Navy in the 50's and used for the first time in the open sea in 1962, was undoubtedly a key technology for successful oil exploration in deep waters (*Freitag and Woods, 1983*). "Saturation" means that after a certain time under pressure, the body fluids and tissues reach equilibrium with the gases in the ambient atmosphere.

Occupational saturation diving systems consist of a network of closed and pressurised steel chambers installed on board a vessel, from which divers are transported to their place of work in the sea by diving bells. The ambient, pressurised atmosphere in the chambers consists of helium, with partial pressures of oxygen of 40 to 60 kPa and carbon dioxide and nitrogen at nominal partial pressures *(Freitag and Woods, 1983)*. Typical working depths in the North Sea are between 50 to 180 m (0.6 to 1.9 MPa). Decompression rates are limited to < 20 m per 24 hours, which means several days of decompression even at moderate depths, resulting in a total saturation period of about three weeks including the three phases of a) compression b) the working period at storage depth and c) decompression. The ambient temperature is higher than normal and is typically around 28-30°C, while relative humidity is kept at about 60% but may reach 80-90% in periods of intense diving activity.

The low temperature at the working depths means that the diver needs to be actively heated in order to maintain his thermal balance. To achieve this, divers wear protective diving suits through which heated (~28^{O}C) seawater is continuously flushed onto the skin. The seawater used for this purpose is taken at the site of operation. No specific treatment such as rinsing or disinfection has been performed besides heating, although in very recent years, UV disinfection, including filtering, has been tried.

1.2 Supporting systems

Obviously, saturation diving demands skilled operation of support systems to ensure the efficiency, safety, health and comfort of the individual diver. These include

technical, physiological, biological and medical tasks, all of which are organised through a diving contractor and performed on board the diving vessel. Vital support systems during the work include gas, hot water to diving suits and communication, all of which are provided by the long umbilical between the bell and the saturation system on the surface.

The on-board gas supply is separated into systems for chamber gas and breathing gas while at work, and due to the high cost of helium, separate systems for gas reclaim are installed. The quality criteria of gas are normally given in terms of pureness with respect to other gases and no information regarding biological/microbiological or chemical purity is required by the authorities. The mixture of helium and oxygen used in the North Sea is supplied as "Diving Quality" and is analysed for its content of helium, oxygen and nitrogen.

Other vital tasks for the diving support team include care of the divers' personal diving equipment such as helmets, masks, oral-nasals and suits.

Tasks of specific importance for performance and comfort, such as fresh water supply, food and daily life management are taken care of by the ship management. Fresh water can either be bunkered ashore or produced on board, the later traditionally based on evaporation, but recently also on reverse osmosis (RO) systems. Water produced by such systems is usually more corrosive than natural fresh water, but the selection of materials for the vessels' pipe work seldom takes this factor into account.

1.3 Health problems related to saturation diving

Exposure to hyperbaric environments is associated with risks of serious acute diseases, such as decompression sickness and arterial gas embolism, the latter as a result of pulmonary barotraumas (*Thorsen, 2003*). Long-term effects have been proposed both regarding neurological symptoms and pulmonary functions surveyed both through experimental and occupational diving on the Norwegian sector (*Todnem et al., 1991; Hope et al., 1994; Skogstad et al., 2002, Thorsen, 2003*). High Pressure Nervous Syndrome, HPNS, is related to pressures beyond the levels used in occupational saturation diving (> 180 msw) but has been studied in experimental diving (*Todnem and Værnes, 1993*).

The most frequently encountered medical problems in connection with diving are ear, nose and throat (ENT) complications (*Molvaer, 2003*). Among these, acute infections of the outer ear have been a well-known and frequent problem in saturation diving since the introduction of the technique back in the late 60's. Outbreaks of infections among several divers at a time have been a frequent cause of costly breaks in operations as described in both the USA and the UK *(Thalmann, 1974; Alcock, 1977).*

Until 1985, there was no world wide public systematic registration of health hazards and complaints in relation to occupational saturation diving. The systematic database initiated by the Norwegian Petroleum Directorate (NPD) at that time, was a pioneering and unique effort. In Figure 1, the injuries included in this database are shown. "Outer ear infections" is the most frequent. The term "Infections" includes skin infections such as folliculitis and abscesses on other parts of the body than the ears. The term "Other health problems/injuries" includes mechanical damage to the

skin and other type of skin complaints. A major complaint in this respect is massive scaling of the skin on palms and soles. This phenomenon is called "Diver's hand" by divers and is a severe and incapacitating disease that affects many occupational saturation divers, while it never has been registered in occupational air diving. As the main problems occur post decompression; i.e. during divers' time off at home, the reporting of this problem was not systematised in the same way as other health hazards.

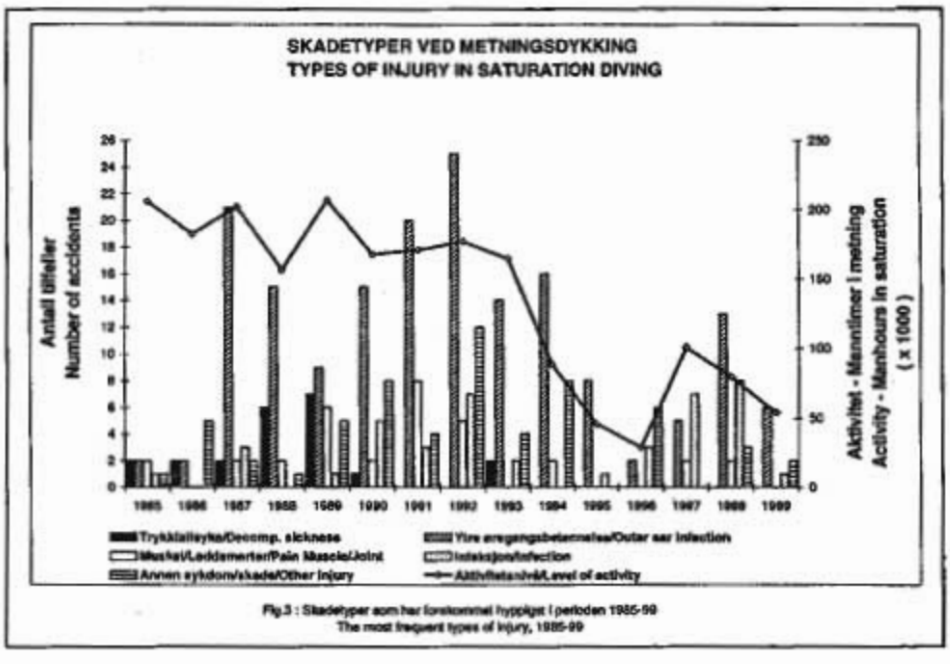

Fig.3 : Skadetyper som har forekommet hyppigst i perioden 1985-99
The most frequent types of injury, 1985-99

Figure 1: NPD database 1999. Types of injury in occupational saturation diving.

To summarise health-related complaints, skin diseases are a major concern in occupational saturation diving.

2. SKIN DISEASES

Skin diseases can be related to mechanical, chemical/toxicological or biological/ microbiological factors. They may be superficial or invasive in deeper skin layers, or both. Superficial diseases affect the upper part of the skin, the epidermis, which is only 0.05 - 0.5 mm thick, and is divided into four layers: stratum basale, stratum spinosum, stratum granulosum and stratum corneum, the last usually known as the horny layer.

The normal skin microbial flora is or outmost importance for prevention of infections (*Noble, 1981; Roth and James, 1988).*

This thesis focuses on superficial skin infections, which can be of either primary of secondary nature (*Chan, 1983)* and which can be caused by most type of microbes, such as bacteria, virus, fungi and parasites.

2.1 Superficial skin infections

Primary bacterial skin infections are the most prominent among superficial infections and are mainly caused by Gram-positive bacteria such as staphylococci and streptococci. (*Trent et al., 2001, Chiller et al., 2001, Sharma et al., 2001)*, of which *Staphylococcus aureus* is by far the most frequently reported skin infectious microbe, as it has been since its first observation by Koch in 1878. This microbe is very common as a normal coloniser of the nasal membranes (*Kloos et al., 1990)* and to some extent also in the normal skin flora, which makes colonisation by *S. aureus* a relevant factor in evaluation of mechanisms behind *S. aureus* skin infections. Group A

Streptococci, GAS, are another frequent gram-positive primary skin pathogen, which in some cases such as Impetigo are as frequently encountered as *S. aureus* (L. Bevanger, personal comm.). This is also a relatively common coloniser of the human pharynx (ca 10%), and has thus a possible endogenous relationship to skin infections. Both of these species are very common in skin infections in warm and humid environments, such as in the tropics (*Bessen et al., 2000*) and in low-hygienic settings, the latter emphasised by community-acquired methicillin resistant *Staphylococcus aureus*, MRSA (*Eady and Cove, 2003*).

Gram-negative primary skin infections are very rare in healthy individuals with intact skin (*Hogan, 1977; Agger et al., 1995*). Secondary skin infections by gram-negatives are common.

2.2 Otitis externa

Infection-related otitis externa is one of the most common ear-nose-throat infections all over the world, (*Walshe, 2001*) and its aetiology has been extensively studied for several decades (*Sentura and Liebmann, 1956*). It is generally accepted, that most cases of external otitis occur in hot, humid environments and rarely in cool, dry climates. Its basic aetiology has not yet been determined, but is currently sharply focused on bacteria. Surveys in the USA and in Israel 30 years ago proved *Staphylococcus aureus* to be the major pathogen (*Feinmesser et al., 1982*) and this was also reported by a study in the Norwegian population (*Dibb, 1991*). In the course of time, however, the major agent has changed and in recent surveys, *P. aeruginosa* has been found to be the dominant pathogenic bacterium (*Clark et al., 1997; Roland et al., 2002*).

3 PSEUDOMONAS AERUGINOSA – an opportunistic pathogen

3.1 The Pseudomonas aeruginosa bacterium

Pseudomonas aeruginosa is the type species of the huge gram-negative pseudomonas genera. Comparison of 16S rRNA sequences has revealed extreme heterogeneity of the traditional group of pseudomonads, and new genera are consecutively established (*Kersters et al., 1996, Anzai et al., 2000*).

P. aeruginosa is a most common bacteria world wide, occurring in fresh- and seawater, soil and on plants although its natural habitat is not precisely defined (*Bergan, 1981*). In fact, the species is notified for its metabolic versatility and its exceptional ability to adapt to and colonize various ecological niches (*Goldberg, 2000*).

The bacterium is strictly aerobic and its ability to grow at 42 °C separates it from most other ubiquitous water-related bacteria. The spectrum of secreted products is huge and includes pigments, bacteriocins, toxins and a broad spectre of enzymes. The production of enzymes and toxins by hospital strains of *Pseudomonas aeruginosa* has been described in detail (*Wretlind et al., 1973*).

The most distinct feature of *P. aeruginosa* is the blue-green pigmentation due to pyocyanins, which has been used both as an identification tool in the laboratory as well as an indicator of the aetiology of cutaneous lesions attributable to

P. aeruginosa; e.g. "green man" (*Hall et al., 1968*) and "green nail syndrome" (*Rhody et al., 2000*). Other types of pigments produced are pyoverdins, pyo-fluoresceins and bilirubins), while a few strains lack pigmentation. The haemolytic effect often seen in older cultures is phospholipase C.

Pyocins are bacteriocins of *P. aeruginosa* produced by more than 90% of *P. aeruginosa* strains. Pyocins are lytic and act as antibacterial compounds vis-à-vis other *P. aeruginosa* and closely related species. Three types of pyocins have been described: R-type-, F-type- and S-type, and each strain may synthesise several pyocins (*Michel-Briand et al., 2002*).

Regarding pigment production and pyocin types, there is no valid evidence for correlation to virulence (*Baltch and Griffin, 1972; Al Dujaili and Harris, 1975).*

P. aeruginosa exo-toxin A has been discussed as a virulence factor due to its lethal, necrotic and cytotoxic effects (*Liu, 1974*), although no significant evidence has been established. A possible role of *P. aeruginosa* exotoxin A gene for the severity of symptoms in patients with otitis externa has very recently been discussed (*Matar et al., 2002).* Another extracellular product with a possible relation to virulence is alginate, which is a major component of *P. aeruginosa* biofilms that protect the bacteria from the host immune response and antibiotic therapy (*Firoved and Derectic, 2003*).

With respect to skin infections, adherence to skin epithelium is a key factor. In accordance with most bacteria, *P. aeruginosa* is shown to adhere to different epithelial cells (*Øgaard et al., 1985*), and in addition, a specific adherence to the external auditory canal epithelium has been suggested (*Sundstrøm et al., 1997*). Furthermore, specific adherence to carbohydrate structures of blood group A, expressed through lectins in the outer ear epithelium has been suggested *(Steuer et al., 1995*).

3.2 Pseudomonas aeruginosa in diseases

P. aeruginosa was first described from wounds by Gessard in 1882, but is generally regarded as a low-pathogen and thus mainly as a nosocomial problem. As such, it is known from a variety of diseases in immune-compromised persons, e.g. those suffering from burns and cancers, and in people with underlying skin diseases, such as self-limited folliculitis and ecthyma gangrenosum (*Bisno, 1984, Greene, 1984; Molina, 1991, Rhody, 2000*). Athlete's foot is another skin disease in which the bacterium causes separation of the horny layer *(Abrahmansen et al., 1983).* The species is less frequent in skin infections in elderly people *(Laube, 2002).*

Beside skin infections, *P. aeruginosa* is a most prominent causal agent to recurrent infections in patients suffering from obstructive lung diseases, such as chronic obstructive pulmonary disease, COPD (*White et al., 2003)* and cystic fibrosis (*Pitt, 2002*). The *P. aeruginosa* strains involved in these infections are often strong alginate-producers (*Hentzer et al., 2001*).

The low pathogenity of *P. aeruginosa* as a skin infectious agent has been demonstrated in experimental studies that attempted at induce infection, and in which infections were produced by most gram-positive and gram-negative bacteria used in the experiments but not by *P. aeruginosa (Singh, 1974).* Despite its low pathogenicity, *P. aeruginosa* is frequently seen in superficial skin infections in certain populations such as swimmers (*Hoadley et al., 1975; Reid et al., 1980*), divers (*Thalmann, 1974, Alcock, 1977*) and people using whirlpool baths and hot tubs *(Gustafson, 1983; Solomon, 1985; Ratnam, 1986; Gregory, 1987;Price 1988; Berger and Seifert, 1990, Zichichi, 2000*). "Swimmer's ear" is the term used for acute diffuse external otitis, which is related virtually without exception to a single bacterial species – *P. aeruginosa (Sentura &Liebmann 1956, Ed. Br Med J 1976; CDC 2000).*

The cause of the frequent presence of this low- pathogen in skin infections in otherwise healthy people such as swimmers, divers and whirlpool users has not been fully determined. Hydration of skin has been suggested as a central parameter from several points of view, among these alterations in the skin bacterial flora *(Marples, 1963, Wright et al., 1972*) and alterations in pH, CO_2 and transepidermal water loss (*Aly et al., 1978*). The shift in microbial flora is suggested as related to removal of ear canal lipids or decreased flow of lipids to the skin surface as a result of increased moisture content *(Sentura and Liebmann, 1956*).

Increased pH will facilitate the establishment and growth of *P. aeruginosa* on skin, as the normal skin pH of 3 is too low for *P. aeruginosa,* whose lower pH limit for growth is 5.5. Increased pH levels up to 8-8.5 will be a selective parameter for the growth of *P. aeruginosa* in its competition with most other water-related bacteria.

Despite failure to establish infections even under provocative experimental conditions *(Singh, 1974)*, experimental studies regarding superhydration of skin and its consequences conclude *P. aeruginosa* to be a main causal of massive dermatitis *(Hoijo-Tomoka et al., 1973). P. aeruginosa* contamination of water related to hydration is rarely discussed in papers dealing with this issue, but is a realistic candidate, knowing the ubiquitous presence of this microbe in tap water *(Jaeggi et al., 1990)*. Even the use of distilled water in experimental skin studies may affect the results in favour of *P. aeruginosa* due to its ability to grow in such water *(Favero et al., 1979)*. The specific role of hydration, therefore, is probably not yet fully known.

Following the documented risk of acquiring outer ear infections from swimming and diving, local prophylactic measures have been introduced *(Thalmann, 1974; Hutchison et al., 1975)*. Such eardrops have been based on acetic acid in various concentrations, with the aim of acidifying the epithelium and thus eliminating colonisation by *P. aeruginosa*. The effect was later related to the acetic acid molecule rather than to acidity as such, as the effect failed to appear with stronger acids *(Irving, 1962)*.

4. EPIDEMIOLOGY

The word epidemiology is derived from the Greek "epi" (on/upon) "demos" (people) and "logia" (study of knowledge). Classic epidemiology comprises the identification of responsible principals or agents (aetiology), sources and reservoirs of these agents, modes of transmission, groups at risk of becoming ill and types of exposure that

predispose to disease. Epidemiological studies involve groups rather than individuals, and the ultimate goal is the prevention and control of disease, rather than diagnosis and treatment.

The differentiation of multiple isolates of the same bacteria or determination of specific relations between the isolates demands molecular epidemiological typing. The basic premise is that epidemiologically related isolates are derived from a single origin and thus differ from epidemiologically unrelated isolates.

Among the most important criteria for epidemiological typing techniques are typeability, reproducibility and discriminatory power. Molecular typing can be classified into phenotyping and genotyping, the former for detection of expressed characteristics in the isolates and the latter for separation at DNA level. Classic techniques for phenotyping include biotyping, antibiotic susceptibility/resistance patterns, serotyping and bacteriocin typing (*Bergan and Midtvedt, 1975; Pitt, 1988*). The most frequently used genotyping techniques are restriction endonuclease analysis of DNA by means of Pulsed Field Gel Electrophoresis (PFGE) *(Tenover, 1995)*, polymerase chain reaction, PCR (*Thiele et al., 1990*) and nucleotide sequence analysis *(Holloway et al., 1992)*.

5. EXPERIENCES PRIOR TO THE THESIS WORK

Field experiences

The initial samplings from divers' ear infections in the Norwegian occupational saturation systems supported earlier findings of *P. aeruginosa* as a frequent causative

microbe and pure-culture isolates were common. However, mixed gram-negative flora including coliforms was not rare, indicating sub-optimal hygienic procedures. Ear infections, caused by *P. aeruginosa* were successfully treated by ear drops containing gentamycin/polymyxins (*Thalmann, 1974; Dibb, 1987*).

The diving contractors put a great deal of effort into the development of strategies, procedures and routines in order to prevent infections. Prophylactic ear drops (Otic Domeboro) were introduced (*Dibb, 1985*) and sharper focus was placed on disinfection and hygiene as preventative tools. Thus, since 1985 and exclusively in the Norwegian sector, a nurse is always on board the diving vessel, helping both to co-ordinate and assist the field investigations as well as to execute the practical implementation of new knowledge.

Microbiological surveys were regularly carried out during operations in order to map microbial contamination within the systems, to investigate the efficiency of various disinfection agents and to evaluate methods and procedures. These surveys were summarized in a *SINTEF report STF23 A91039 "Programme for Research and Development in Diving Technology (FUDT) - Bacteriology 1988-1990. A summary"*. These field surveys enabled occupational procedures to be gradually upgraded, while specific guidelines for disinfection and hygiene were drawn up and reported *(Ahlén et al., 1991)*. Guidelines for a simple method of field microbiological sampling were also described *(Dibb, 1992)*.

Laboratory analyses/experiments on field-related P. aeruginosa

The microbial material from the diver's infections and environment was consecutively analysed by routine biotyping including species determination by API 20NE (BioMerieux, France) and antibiotic resistance testing to Gentamycin/Polymyxin in relation to its use in field treatment. For further discrimination, serotyping was performed on all *P. aeruginosa* isolates. Serotyping is based on major antigens expressed by lipopolysaccharides (LPS) in the outer membrane of the cell wall, and *P. aeruginosa* serotyping was first introduced by *Aoki et al., 1926*. Researchers subsequently formed their own serotyping schemata, making comparison of results between studies impossible. A reference method based on an international serogrouping schema of seventeen O-serotypes (International Antigenic Typing System, IATS) was prepared *(Liu et al., 1983)* and later extended to include a further three antigens. *(Liu et al., 1990)*. This serotyping method has been the "gold standard" for epidemiological studies of *P. aeruginosa*. Traditionally, serotyping has been performed by means of polyclonal antisera and the typeability using this method varies from 85-95% to 45% *(Walia et al., 1988)*.

Early observations of a growth-inhibiting effect from some infectious-related *P. aeruginosa* directed towards species from the normal ear flora was analysed with respect to known extracellular substances, such as pigments, pyocins and enzymes (unpublished data) and was also evaluated with respect to earlier described "antibacterial" compounds (*Zyskind, 1965; Machan et al., 1991*). As the phenomenon did not match any of the factors evaluated, it was attributed antibacterial factor, ABF.

Unlike the data reported by Alcock, 1977, the freshwater systems on board occupational diving vessels were seriously contaminated with *P. aeruginosa.* Use of plastic materials (e.g. PVC) in the fresh water buffer tanks to the chambers were suggested to be of ultimate importance in this respect, as PVC is shown to favour attachment and growth of *P. aeruginosa* (*Pedersen et al., 1986*). Upon further evaluation, the traditional water production systems used include several factors which may favour growth and survival of *P. aeruginosa,* such as evaporation temperature of 42°C and anticorrosive treatment by alcali to pH 8-8.5 (*Ahlén et al., 1987).*

The presence of the same serotype patterns in fresh water and infections indicated a potential environmental role for the *P. aeruginosa* isolates in the infections.

AIMS OF THE THESIS

Following implementation of better strategies, procedures and routines for prevention, a reduction in skin infections was seen during the first years of the NPD registration programme (1986-1989). On further evaluation this reduction was found to apply to a reduction in mixed infections involving gram-negatives including coliforms, i.e. infections related to limitations in the hygienic features of the diving systems. However, outbreaks of pure culture infections with *P. aeruginosa* were subsequently reported. In this situation, the natural challenge was to identify the sources and manner of spreading of the infectious pure-culture isolates of *P. aeruginosa* and to enable strategies for elimination to be developed or at least to minimise their presence in the occupational diving systems, i.e. an epidemiological challenge. This raised the following questions:

a) What are the risk factors involved in acquiring skin infections during saturation?
b) Are some *P. aeruginosa* isolates a greater infectious threat than others?
c) Are there specific habitats for infectious isolates in occupational diving systems?

"Diver´s hand" (DH) has not been described elsewhere and its aetiology is unknown. Topics to be studied regarding this phenomenon were:

a) Mapping of extent of DH among occupational divers.
b) Description of clinical picture and histological investigations for epidemiology and mechanisms.

SUMMARY AND DISCUSSION

At the time of our introduction to occupational saturation diving in 1985, the increased risk of acquiring outer ear infections was well known to both operators and divers (*Thalmann, 1974, Alcock, 1977*). However, no written data on the occurrence or frequency of such infections at an occupational level were available from the Norwegian sector of the North Sea. Moreover, the main causative agent was well known as the "pyo" bacterium, a nickname for *Pseudomonas aeruginosa*. In spite of the fact that the infections developed during saturation periods, and therefore were likely to be related to the occupational environment, the leading theory regarding sources and spreading was that the diver himself introduced the infectious agent, a theory adopted by several authors *(Alcock, 1977; Bell, 1985)*. Local prophylactics in form of acetic acid ear drops (Otic Domeboro) and local treatment (Gentamycin /Polymyxins) were thus used empirically and at a personal level.

The theory of divers as carriers of infectious pseudomonas strains was in contrast to common knowledge that the normal skin flora does not contain pseudomonas (*Noble, 1981*) and verified also in a Norwegian healthy population *(Dibb, 1990)*. The fact that pseudomonas is seen in less than one percent as transient flora in normal ears even in tropical and subtropical climates *(Sentura and Liebmann, 1956)* made the theory even more doubtful.

The detection of infectious strains in the environment made identification of reservoirs and sources a matter of priority. The tools available for such discrimination within the *P. aeruginosa* species were all phenotypic with serotyping as the "golden standard". As mucoid strains of *P. aeruginosa* are very rare in our material, serotyping

by use of polyclonal antisera was a successful tool (> 75%). The serotyping of *P. aeruginosa* showed a limited serotype pattern in diver-related infections compared to hospital infections (Paper I). A limited spectrum of five serotypes was obtained from divers' infections (n:120) compared to ten serotypes from hospital infections (n=45). The dominance of certain serotypes in diver-related infections is exemplified by serotype O:11, which was represented in 45% of the divers infections compared to 7% from hospital infections. The dominance of serotype O:11 was also seen in the environmental and fresh water samples from the saturation systems. This was our first indication of a possible role of environmental factors in *P. aeruginosa* infections in this particular occupation.

Dominance of serotype O:11 has been reported from clinical and environmental studies around the world, both community-acquired infections as well as folliculitis in water-related activities , e.g. swimming pools and whirlpool baths *(Highsmith et al., 1985.; Tassios et al., 2000)*, the latter reporting multidrug resistance in strains of this serotype.

The dominance of serotype O:11 was a serious limit in the suitability of serotyping as a tool to address our concerns. A combination of phenotyping methods, with serotyping as a primary screen and use of pyocin typing for finer discrimination between isolates has been recommended *(Pitt, 1988)*. As pointed out above, pyocins are lytic and are solely directed at other pseudomonads. Our observations of an antibacterial factor from *P. aeruginosa* from divers' skin infections (Paper I) were thus not understood to be a pyocin compound, as its effect was directed towards skin normal flora and no lytic effect could be seen. As the antibacterial factor, ABF, was

observed in divers' skin infections and not in the corresponding clinical infections investigated in parallel, we assumed ABF to be a plausible additive epidemiological marker in combination with serotyping in this specific occupation. However, even if all the diver-related infectious isolates of serotype O:11 expressed ABF, only a small percentage of serotype O:11 from the environment were positive with respect to this antibacterial activity (unpublished data) and this strongly demonstrated the restriction of serotyping as an epidemiological tool in this occupation.

A breakthrough in our epidemiological work was made in 1994 by the introduction of novel genetic techniques, based on restriction enzyme fragmentation of DNA together with new approaches of electrophoresis. The novel techniques using rare-cutting restriction enzymes *(McClelland et al., 1987)* and the recently developed method of pulsed field gel electrophoresis, PFGE (*Chu et al., 1986; Clark et al., 1988*; *Lai et al., 1989)* had been demonstrated as very successful for distinguishing of bacterial isolates and are currently a very well-known and approved technique.(*Speert, 2002*). Plausible candidates for rare-cutting endonucleases suitable for *P. aeruginosa* had been described (*Römling et al., 1990)* and the potential of this method was readily shown by its use in genome size determination of *P. aeruginosa* (~6000 kilobases) (*Hector et al., 1990; Ratnaningsihm et al., 1990).*

Five rare-cutting enzymes were tested on a selection of *P. aeruginosa* isolates from our biobank, DraI, XbaI, AsnI, SspI and SpeI, the latter the most appropriate for our purposes, as exemplified in Paper III, Figure 4. The combination of SpeI and PFGE had been shown to be a very useful tool for whole genome analyses of *P. aeruginosa* PAO *(Holloway et al., 1992)* and has been the "gold standard" in our epidemiological

work in occupational saturation diving. Interpretation of the DNA restriction patterns produced by PFGE results and the criteria for bacterial strain typing has been done in compliance with the recommendations by *Tenover, 1995.*

The potential of this new tool was clearly demonstrated by a retrospective mini-epidemiological study (Paper I). The twelve skin infections analysed could be separated into five different PFGE genotypes consecutively coded from A to E. The reservoirs of two of the infectious genotypes were demonstrated by their presence in the freshwater systems prior to the infections (D and E). Although not identified in the environment on that particular occasion, genotype A has since been demonstrated in both freshwater and gas systems on board diving vessels. The sources/reservoirs of genotypes B and C were not identified nor have they been seen since.

The inadequacy of serotyping in our context was strongly demonstrated by the PFGE analyses referred to above. The shared serotype O:11 pattern in the genotypes, A, B and E was later verified in many additional genotypes. This was exemplified, but not specified, in Paper II, Figure 1, which show twenty different genotypes of serotype O:11. The heterogeneity of serotypes among genotypes has since been reported in other studies (*Muller-Premru M et al., 2000*).

Genotypes D and E are the most frequent genotypes in infections and in the environment (Papers II and III). The longitudinal presence of more than ten years by now (Papers II and III), indicate environmental promotion of growth and survival, as also is of relevance for the other frequent infectious genotypes N, AD and AU (Paper III).

The longitudinal demonstration of the same genotype is a confirmation of both the typeability and reproducibility of the method used. The distinct PFGE patterns make discrimination of the genotypes easy (Paper III, Figure 3) and this demonstrates the good discriminatory power of the method. Based on this, it is not likely that there are close family relationships between these frequent genotypes. Macro-restriction fragmentation of the *P. aeruginosa* genome has shown highly diverse patterns (*Römling et al., 1994*). This versatility has been further strengthened in recent studies, which demonstrate whole-genome sequence variation among multiple isolates of *P. aeruginosa* (*Spencer et al., 2003*).

Despite the subsequent implementation and acceptance of the results of our studies, which strongly suggested an environmental role for these infections, divers were still being accused of being the source and carrier of the contagious agents into saturation systems. This was especially a problem for divers getting recurrent infections and in fact, cases of divers being excluded from diving operations due to recurrent infections have been reported. Such a case was analysed by retrospective PFGE analyses of the genotypes present in infections in a single diver in 1989, 1990 (twice) 1996, 1997 and 1998 (Paper II). The known, established environmental genotypes AAA, D and N were identified as causal agents in four of the six recurring infections. With reference to the postulated positive correlation between the occurrence of external otitis and blood group A (*Steuer et al., 1995*), we did not find such a correlation in our material, and it is worth mentioning that the diver referred to above has blood group O.

The role of the frequent infectious genotypes in infection outbreaks i.e. infections in several divers during a shorter period of time has been demonstrated by several cases (Paper III). With the exception of genotype BM, all outbreaks have been caused by environmentally related frequent appearing genotypes (Papers II and III). Lack of environmental identification for BM might be related to the fact that regular environmental control had not been introduced on all vessels by the time of its occurrence. Genotype AAA is another outbreak –related genotype with short periods of presence in the saturation environment (Paper III).

The role played by divers' personal equipment in the survival of infectious genotypes is exemplified by the outbreak of infection in spring 1997 and the subsequent isolation of the specific genotype throughout the summer (Paper III). The genotype responsible was identified from the freshwater supply in connection with the outbreak, and was spread to the equipment by the cleaning procedures employed; in fact, it was found in the diluted disinfectants in use in the diving bells; i.e. spreading from the fresh water used as diluents.

Based on our studies, we regard the fresh water system as the most potential reservoir for infectious genotypes in saturation systems. Further PFGE analyses have shown that all the frequent infectious genotypes D, E, N, AD, AU and AAA have been identified from these systems (Paper III, Figure 2), most of them for long periods of time. However, presence in fresh water systems has also been shown for a number of other *P. aeruginosa* genotypes from single infections as well as genotypes never shown to be infectious. This is in agreement with our earlier statement assuming freshwater systems on diving vessels to promote growth of *P. aeruginosa*.

The fact that only a few of the genotypes present in these systems over time are frequent in infections indicates that other factors than growth and survival might be of importance. This is further strengthened by the fact that some established genotypes never have been seen from infections in spite of their persistence in freshwater systems. Genotype G is such a genotype, having been found in freshwater systems and the environment for seven years but never isolated from infection (Paper III).

Most of the fresh water used on board diving vessels is produced from seawater, which may point towards seawater as a plausible source of microbial contamination. This has been demonstrated to some extent by genotype N (Paper III, Table II) and later upon further retrospective analyses genotypes, D and E (unpublished data). Isolation from seawater, however, is very rare, and the fact that many other *P. aeruginosa* genotypes have identified throughout the surveillance period (Paper III, Table 1) suggests that a general or frequent occurrence of the infectious genotypes in seawater is not likely.

The potential role of seawater as a source to infectious genotypes was clearly demonstrated by the field study (Paper IV), in which subsequent and almost daily contamination of new *P. aeruginosa* genotypes from seawater was seen. However, only genotype TP12 managed to invade the vessels' freshwater production and supply systems and produce infections (Paper IV). This strongly strengthens the hypothesised selective preference of some genotypes in these systems, which also may reflect the presence of the infectious genotype TP2 throughout more than four months surveillance. The fact that none of our earlier identified *P. aeruginosa* genotypes were

observed in this field study may be explained by the character of the operation in which pipe-laying in earlier un-explored areas was the main activity, and may be an indication of a geographically restricted distribution of the frequent infectious population.

Other skin problems

"Diver's hand", DH, the severe and incapacitating skin scaling in palms is strongly related to saturation diving. This statement is based upon the facts that DH is unknown to air divers both offshore and onshore and that none of the affected divers had experienced the phenomenon prior to their first saturation. The aetiology remains unknown.

Due to the frequent occurrence of *Pseudomonas aeruginosa* in various skin infections (otitis externa and folliculitis), the microbe was as well surveyed with respect to DH. Field studies of microbial flora of palms were performed throughout several saturation periods *(STF23 A 91006, SINTEF report 199, unpublished).* Dominance of gram-negative rods including coliforms and infrequently including *P. aeruginosa* was found in both DH positive and DH negative divers. On behalf of the divers' requests, further evaluation of a possible role of *P. aeruginosa* was done by prophylactic treatment (acetic acid solutions). No significant differences were seen with respect to DH development (unpublished data).

DH symptoms in relation to other known skin diseases such as "Recurrent focal palmar peeling" caused by streptococcae and staphylococcae and "Keratolysis exfoliativa" were evaluated as were fungi and algae (*STF23 A94056, SINTEF report*

1995, unpublished). "Pitted keratolysis" was another disease evaluated (*Zaias et al., 1965*).

The extended studies including histological examinations (Paper V) showed no significant signs of inflammation or known pathogens. The study concluded decompression as being of no or little relevance, as DH development occasionally were demonstrated during compression and commonly during bottom time.

Recent literature regarding skin scaling as a result of water exposure as such suggests that extended water exposure for 4 to 24 hours results in a three- or four-fold increase in the thickness of the stratum corneum. This in turn leads to extensive disruption of the intercellular lipid lamellae of the stratum corneum (*Warner et al., 2003; Bouwstra et al., 2003)*. The plausible role of water exposure as such may be discussed, as all divers are exposed to water for long periods, but not all suffer from DH. Additional factors are therefore believed to be of importance.

Recent publications on *Kytococcus sedentarius* as the causal agent of "pitted keratolysis" (*Longshaw et al., 2002*), together with frequent observations of the same microbe in gas supplied for saturation diving (*SINTEF report STF 78 2002*, to be published) could indicate that this microbe may play a role in the development of DH.

In view of this new information, a retrospective pilot study of stored DH material from our bio-bank was carried out during spring 2003 (Draft enclosed- Appendix A). The detection of *Kytococcus sedentarius* in samplings from palms of divers suffering from DH indicate that also this skin problem may be related to microbes as a causing agent.

CONCLUDING REMARKS

This thesis is a summing-up of my work on the identification and prevention of skin infections in the special field of occupational saturation diving in the North Sea. Since the start in 1985, the studies have consistently pointed in the direction of an environmental role in such infections, and in particular towards contamination of diving vessel freshwater systems, a viewpoint which has been confirmed by retrospective genetic studies.

The exclusive role of a certain *P. aeruginosa* genotype population in skin infections in occupational saturation divers is strongly underlined by the fact that only 2 % of the *P. aeruginosa* genotypes identified (8/332) are responsible for most infections and for all the registered outbreaks. The fact that the frequently infectious genotypes persist within saturation diving systems for years in spite of that new genotypes are steadily being introduced is noteworthy, and demonstrates, that a minority of genotypes displays a specific preference for this habitat and thus exert a constant pressure on the development of infections. This is further substantiated by the fact that these particular strains are only rarely found in seawater, which has been shown to be a probable source.

The aetiology of "Divers hand" remains unknown. The recent identification of the role of *Kytococcus sedentarius* in skin scaling symptoms may be worth further evaluation.

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APPENDIX
A

Kytococcus sedentarius – a possible contributor to "Diver's Hand"

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Introduction

Occupational saturation diving is a widely used technique for installation and maintenance of offshore sub-sea petroleum production systems in the North Sea. T occupational living and working environment is biologically unique (1,2) with pressurised atmosphere of helium and oxygen and increased temperature and humi levels. One major consequence of this exposure is increased frequency of various s disorders. The main skin problems are otitis externa and folliculitis, caused by *Pseudomonas aeruginosa* (1,2,3,4,5). Another frequent skin disorder takes the forn extensive skin peeling of the upper layers of the skin of the palms and occasionally soles of the feet, and is attributed "Diver's hand", DH (6). The aetiology of DH is r known.

Regarding the skin infections caused by *P. aeruginosa*, systematic environmental monitoring has shown that the saturation diving environment harbour a few freque infectious strains, some of which for more than ten years. Recent investigations of biological contamination of the gas used for pressurising chambers and breathing g work have shown gram-positive contamination of the gas supply (7). A common contaminant seen in these investigations is *Kytococcus sedentarius* (former *Microc sedentarius* (8), which very recently has been described as a potential etiological a "pitted keratolysis" (9), a skin peeling disorder known from the clinics. The hypotl related to two strong keratin-degrading enzymes in this bacterium.

The plausible role for *K. sedentarius* in DH has been evaluated in a retrospective p study on DH materials from our biobank (2).

Materials and Methods

The microbiological material used in this pilot study is obtained from palms and divers in the period between 1988 and 1991, collected in our bio-bank. All diver included in this pilot study have experienced DH at one or several occasions, alt the statuses regarding DH development at the time for these samplings are not v

Identification of *K sedentarius* is based on bio-typing and phenotyping includin biochemical typing (API systems), pigmentation and methicillin-resistance. The *K. sedentarius* strain used by Longshaw et al (9) was kindly donated by the autl used as a reference in all typing.

Results

Kytococcus sedentarius was identified from palms and soles of four of the elev included, exemplified in Figure 1, showing the microbiological status in diver n samplings taken at the end of decompression show dominance of *K. sedentariu* palm of the left hand and sparse presence in both soles. The other sampling spo ears and axillae) showed mixed cultures of *Micrococcus luteus* and *Micrococc* which together with coagulase-negative staphylococci, CNS, were prominent i in the rest of the investigated samplings.

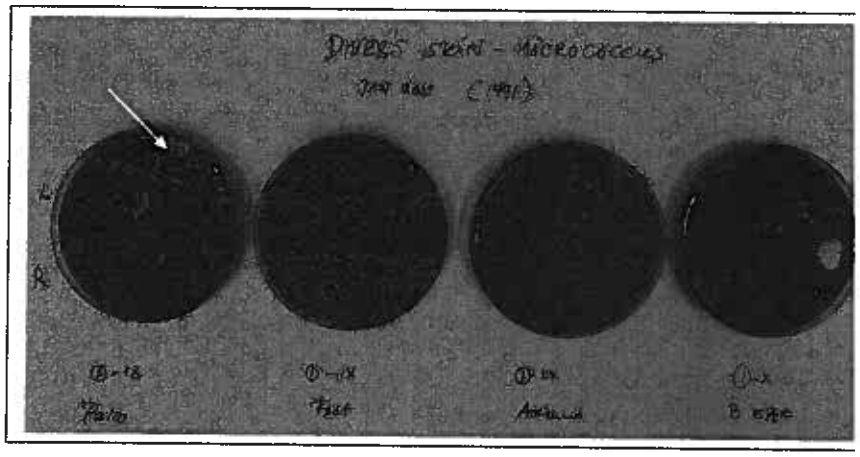

Figure 1: Skin microbial flora on palms, soles, behind ears and in axilla in a saturat diver during decompression. *Kytococcus sedentarius* (marked with white arrow) is dominant on left palm and is sparse on soles.

Discussion

The presence and even dominance of *K. sedentarius* on some of the palms investig new information, as was the pronounced presence in the diving gas quads. The bac has not been sub-typed earlier in our studies due to the universal presence in norma flora. Thus, the extensiveness of this bacterium in occupational saturation systems known. Retrospective investigations of a limited number of occupational chamber atmosphere samplings show presence of *K. sedentarius* in all of the analysed sampl (day 4, day 6, day 16, day 18 and final decompression on day 21) i.e. throughout th whole saturation period.

Some of the *K. sedentarius* strains in our pilot study show all the phenotypic featur the reference strain from the referred publication (9) while other seem to differ. Thi could imply that strong keratin-degrading strains as described by Longshaw may h been present in the chamber gas atmosphere.

The outcome from the strong keratin-degrading strains of *K. sedentarius* in "Pitted keratolysis" seems not to be of full relevance for DH. Nevertheless, the observation be worth further investigations of possible relations between the scaling phenomen specific strains of *K. sedentarius*, including both phenotyping and genotyping.

In conclusion, the recent publication from Longshaw et al (9) and the new observat of the strong keratin-degrading *K. sedentarius* both in gas supply, diving chamber g atmosphere and on palms and soles of divers suffering from DH may indicate a pos contribution to the saturation-related skin disorder DH; i.e. another skin infection problem in this occupation.

Acknowledgements

We wish to thank Statoil, Norsk Hydro, Esso Norway, the Norwegian Petroleum Directorate and Stolt Halliburton Joint Venture for financial support. We also thank Gardner Cryogenics for skilled co-operation during the gas investigations.

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2001

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2002

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2003

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