Forward

As a joint meeting of the International Rhinologic Society, the International Symposium on Infection and Allergy of the Nose, and the Japan Rhinologic Society, it is not an overstatement to declare that the 1991 International Congress of Rhinology (1991 ICR) was possibly the greatest congregation of rhinological professionals in the world.

The oldest of the participating societies, the International Rhinologic Society is comprised of rhinologic societies in Asia, North and South America, and Europe and publishes the journal *Rhinology*. The Japan Rhinologic Society was celebrating its 30th anniversary as the world's largest rhinologic society with over 2,300 members. Our other partner in the congress, the International Symposium on Infection and Allergy of the Nose, held its tenth symposium since 1976. Since the first congress held in Tokyo, this symposium has been hosted by a variety of nations and enjoys a truly international flavor. Having been involved in this symposium since the beginning, we were particularly pleased with its progress.

The IRS has held 14 meetings since 1957. However, from the beginning these meetings were held solely in North America and Europe under the initiative of M. Cottle's group. They consisted primarily of postgraduate seminars on functional nasal surgery. When the JRS jointed the IRS in 1981, we proposed that the IRS expand its activities and offer not only postgraduate courses, but an international congress as well which would include all rhinological fields and accept free paper presentations from all over the world. Our proposal was accepted and the 1991 International Congress of Rhinology in Tokyo was organized based on this idea. This congress provided an incredible opportunity to exchange research findings with 860 participants attending from 34 countries. For six days almost every topic of rhinology was discussed by outstanding specialists from around the world. The pace of recent scientific progress made this exchange of information invaluable.

We would like to thank all those who have taken such an active interest in this congress and without whom it would have been impossible to achieve. The cumulative knowledge and experience of the specialists who gathered at this congress hold a great deal of potential. We are proud to offer you the results of your work.

Ryo Takahashi, M.D.
President
International Rhinologic Society

Shunkichi Baba, M.D.
President
10th International Symposium on Infection and Allergy of the Nose

Tetsuo Ishii, M.D.
President
30th Annual Congress of Japan Rhinologic Society

Minoru Okuda, M.D.
General Secretary
1991 International Congress of Rhinology

His Imperial Highness, Prince Tomohito of Mikasa, delivers a speech at the opening ceremony.

Dr. Keiichi Tanaka delivers a welcome lecture.

Entertainment provided, included a Noh play before the banquet.

CONTENTS

Welcome Lectures

Symposia

1. Mucosal Immunity of the Nose

2. Pathophysiology of Nasal Allergy

3. Up-to-date Medication for Allergy and Infection

The following papers are omitted due to authors not submitting their work.

Welcome Lectures

Medical Technology and Its Future
Yasuhisa Sakurai *Japan*

Symposia

Canpo Drugs for Nasal Diseases
Z. Zhang *P.R.C.*

Magnetic Resonance Imaging
K. Oyama *Japan*

Diagnosis and Repair of Skull-Base Fracture
G. Oberascher *Austria*

Summary of the Fireside Conferences

Biochemistry of Nasal Fluids
H. Deuschl *Sweden*

Welcome Lectures

ULTRAHIGH-RESOLUTION SCANNING ELECTRON MICROSCOPY AND ITS APPLICATION TO MEDICAL RESEARCHES

K. TANAKA

Dept. of Anatomy, Faculty of Medicine, Tottori University, Yonago, Japan

INTRODUCTION

Since the scanning electron microscope (SEM) first became available for practical application, it has been widely used for medical researches, because SEM provides vivid seemingly three dimensional images. However, the SEM has been used mostly for study at low magnifications, such as surfaces of cells, tissues and organs, with little attention given to high resolution fields. Though the reason was, in one aspect, due to lack of good specimen preparation techniques, it was essentially based on the inferiority of the resolving power of SEM. In 1985 we,together with Hitachi Ltd., developed an ultrahigh-resolution SEM called UHS-T1 (1,2). It was equipped with a field emission gun and an objective lens with a very short focal length and it showed a resolution of 0,5 nm. With this instrument not only intracellular structures but also viruses and biological macromolecules were clearly observed. On the other hand, specimen preparation techniques have been progressively improved. For observing intracellular components, we devised in 1981 the osmium-DMSO-osmium method (3). By the method various intracellular membraneous structures, such as endoplasmic reticulum, mitochondria, Golgi complex,were clearly disclosed in three dimensions, because the excess cytoplasmic matrices could be removed from the surface of previously fixed cells by a maceration procedure with a dilute osmium tetroxide solution. For observation of very tiny specimen as biological macromolecules we also devised the carbon plate method (4). In the specimens prepared by this method the objects could be observed without metal-coating which markedly distort the fine structures. By the method, ferritin, immunoglobline, hemocyanin,thyroglobulin and so on were successfully observed (5).
In this paper an outline of the ultrahigh-resolution SEM, techniques for specimen preparation, findings of the specimens prepared by these methods, are described.

SEM INSTRUMENT (UHS-T1)

The main production design specifications are as follows :

Electron optics
Electron gun : field emission electron source.
Accelerating voltages : 1 - 30 kV.
Magnification : 150 - 1,000,000 X.
Lens system : 2-stage electromagnetic lens system.
Objective lens : f 3.6 mm ; Cs 1.6 mm ; Cc 2.0 mm.

Vacuum system
Gun chamber : ion pump (60l/s)X1.
First intermediate chamber : ion pump (20l/s)X1.
Second intermediate chamber : ion pump (20l/s)X1.
Specimen chamber: 2 turbomolecular pumps (340l;60l/s) and rotary pump (174l/min)X1. (They are connected in series)
Specimen exchange chamber : turbomolecular pump (60l/s) X1 and rotary pump (174l/min)X1.

Anti-contamination devices
Cold finger located close to the specimen stage X1.
Cold trap located over the first turbomolecular pump of the specimen chamber X1.

The diameter of the electron probe was calculated to be 0.45 nm at 30 kV, and a probe diameter of 0.5 nm was confirmed by observation in STEM mode. In observation of a biological material coated with platinum, the SEM showed 0.5 nm resolution.

PREPARATION METHODS

1. Aldehyde-prefixed osmium-DMSO-osmium method (6)
This method was used for observation of intracellular structures.
Aanimals were perfused with physiological saline solution to remove the blood, then perfused with a mixture of 0.5% glutaraldehyde and 0.5% folmaldehyde in M/15 phosphate buffer solution, pH 7.4. Small blocks of tissues were removed from the animal. The blocks were fixed with 1% osmium tetroxide solution for 1 - 2 hours. After having been rinsed with a buffer solution (pH 7.4) they were immersed in 25% and 50% DMSO solution for about 30 min each. The specimens were frozen on a metal plate which had previously been chilled with liquid nitrogen, and cracked into two with a razor blade and a hammer. The cracked pieces were immediately placed in a 50% DMSO solution for thawing at room temperature. After rinsing , the specimens were postfixed in 1% osmium tetroxide for 1 - 2 hours, then transferred to a 0.1% osmium solution, and left standing for about 3 days at 20°C. The specimens were then conductively stained with a 2% tannic acid and 1% osmium solution. After this step they were treated by routine methods.

2. Carbon plate method (4)

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2. Carbon plate method (4)
This method was used for observing very tiny

specimens such as viruses or macromolecules. Droplets of the materials were placed on carbon coated carbon plates (CC plates) and left for 1 - 3 min. The CC plates were made by slicing commercial carbon rods and polished with fine polishing films. After boiling in distilled water for about 10 min to remove oil, the CC plates were vacuum evaporated with carbon on their surface and were made hydrophilic by irradiation overnight with UV light. The specimens were briefly rinsed in distilled water and impregnated with a heavy metal salt such as uranyl acetate, phosphotungustic acid and osmium tetroxide mordanted with tannic acid. The specimens were briefly rinsed in distilled water and the excess fluid was blotted off with filter paper. They were then plunged into liquid ethane for rapid freezing. The frozen specimens were transferred into liquid nitrogen and dried in a freeze dryer with a turbomolecular pump. The dried specimens were observed with the ultrahigh-resolution SEM without metal-coating.

RESULTS

1.Membraneous intracellular structures

When specimens prepared by the aldehyde prefixed O-D-O method were observed by SEM, various membraneous intracellular structures were seen in three dimensions (Fig.1). Rough endoplasmic reticulum usually consisted of flattened cisternae of various

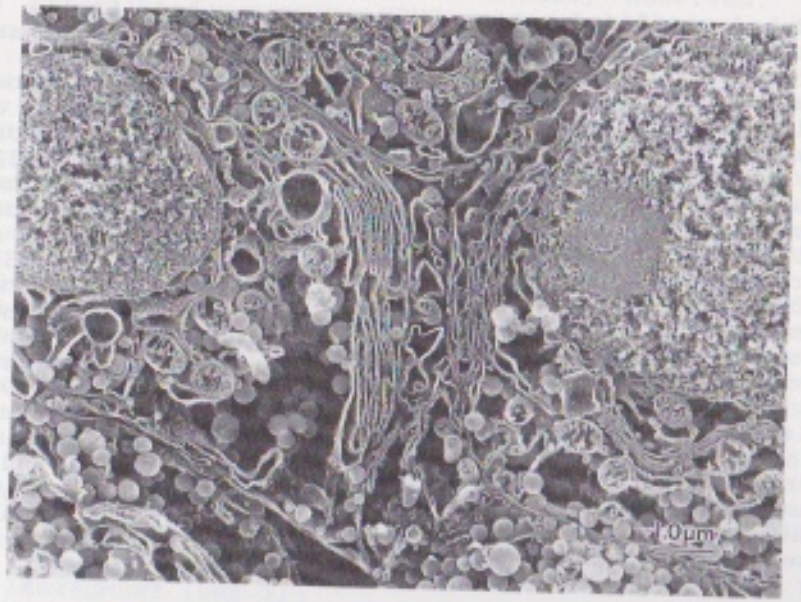

Fig.1: Intracellular structures of rat anterior pituitary gland cells. From Tanaka et al (7).

sizes, arranged in parallel, the surface of which were studded with many ribosomes. Though these cisternae were seen separately in TEM pictures, they were seen to be jointed together in some manner in SEM pictures. In particular, Nissl bodies showed a complicated branching network. On the cracked surfaces of mitochondria the characteristic internal organization could be stereoscopically seen. The mitochonda were bounded by two sheets of unit membrane and the inner membrane projected into the interior of the organelles to make mitochondrial cristae of lamellar, tubular or vesicular shape. In Golgi complex of a rat lacrimal gland cell, we observed that the stacks were all linked by anastomosing branches extending throughout the cytoplasm,forming an irregular network. On the other hand, connection between Golgi stacks and rough ER was often observed in nerve cells, though a controversy concerning the existence of such connection continues. In a rat motor nerve cell, a tubule arising from rough ER extended to the Golgi stack and fused mostly on the cis-most cisternae.

2.Viruses and biological macromolecules

Viruses are very suitable for study by the ultrahigh-resolution SEM, because the preparation technique is very simple and they are not so small as biological macromolecules, for which highly skilled SEM operating technique is required. We could observed AIDS virus (fig.2) and Vaccinia virus at very high magnifications (7).

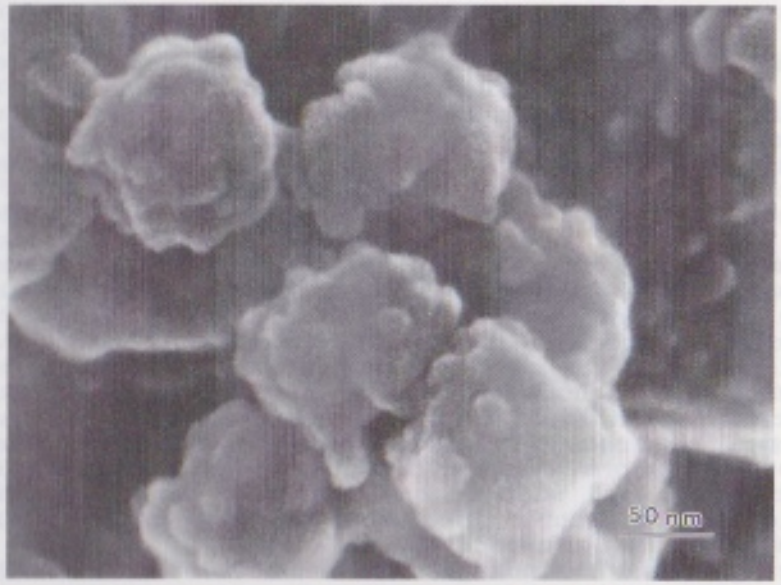

Fig.2:AIDS-viruses budded from a cultured lymphocyte.

For observing macromolecules skill is necessary for operating the SEM apparatus, because the subjects are extremely small, and photographs must be taken at very high magnification in avoiding contamination.
The hemocyanin appeared as hollow cylinder, circular in cross-section with a quadrilateral longitudinal profile. Higher magnification views of the circular face showed a collar and a central hole, but central caps were not found. IgG was observed as a complex of three rounded bodies. The central body might correspond to the Fc fragment and the two side ones might correspond to Fab fragments. Each fragment was divided into two subunits and one subunit of the Fc seemed to be bound to one subunit of Fab with a filament to form a heavy chain. The other subunits of the Fab might correspond to a light chain. Thyroglobulin molecule appeared as a roughly spindle-shaped body. It consisted of two three-cornered subunits. In addition, ferritin, apoferritin, immunoglobulin M, compliment Clq, actin filament, DNA double felix and proteoglycan were clearly observed by using the carbon plate method.

DISCUSSION

Until recent years, SEM has been regarded as instruments for observing only the surface of cells and tissues. However this idea should be discarded after the development of the ultrahigh-resolution SEM (UHS-T1). With this SEM not only intracellular structures but also viruses or biological macromolecules became to be easily studied. On the other hand, some unexpected problems came to fore with improvement of instrumental resolution in the area of specimen preparation. The biggest problem was how to give conductivity to specimens. Usually they were coated with metal in ion sputter coaters or evaporaters. On observation with the ultrahigh-resolution SEM, metal particles coated on specimen surfaces were plainly seen as round "pebbles", although they were not discerned with ordinary SEM. Then we used uncoated but conductively stained specimens and obtained fairly good results. When specimens were very small, however, their sizes became notably larger by decoration with the tannin-osmium complex produced during the conductive staining. For such tiny specimens, therefore, observation without metal-coating and without conductive staining must be the best. To this end, we developed the carbon plate method. Using this method we could observe many biological macromolecules in good contrast and without any charging. However, this technique was applicable only for very small specimens such as macromolecules.
Following these findings, we concluded that the method for imparting electrical conductivity to biological specimens should be adapted according to the size of the specimens, that is, the coating method by the ordinary sputter-coater is suitable for objects bigger than cell organelles; the conductive staining is effective for objects ranging in size from cell organelles to ribosomes; and for biological macromolecules uncoated and nonconductively specimens should be used.

SUMMARY

By the development of an ultrahigh-resolution SEM,the resolution of SEM was markedly improved. Concerning specimen preparation, the osmium-DMSO-osmium method, which is effective for revealing intracellular structures, and the carbon plate method for observing smaller objects such as viruses and biological macromolecules were devised in recent years. With the improvement of instrumental resolution and specimen preparation techniques, the SEM has become a powerful tool for studying ultrastructure in biomedicine.

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DRUG RESISTANCE IN BACTERIA
HISTORY, GENETICS, BIOCHEMISTRY

S. MITSUHASHI

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Before the introducion of chemotherapeutic agents for bacterial infections, pneumonia, tuberculosis and other bacterial infections were the most common cause of death in human beings. Paul Ehrlich described, in 1904, the trypanocidal activity of p-rosaniline soon after the start of experimental chemotherapy in Germany. G. Domagk discovered prontosil, which was the first chemotherapeutic agent for gram-positive bacteria. After the discovery that sulfonamide (SA) was the active component of prontosil, SA constituted the first epoch of antibacterial chemotherapy. The discovery of penicillin by A. Fleming in 1929 led to the second epoch of antibiotic research in chemotherapy, and was followed by streptomycin (SM), chloramphenicol(CM) and tetracycline (TC). These findings caused revolutionary changes in the search for antimicrobial agents by broadening scope of research materials, i.e., soil, water, air, dust, etc. in addition to man-made chemotherapeutic agents by organic chemistry. Mortality due to pneumonia decreased rapidly after the introduction of chemotherapeutic agents. Similarly, the numbers of deaths attributed to osteomyelitis, carbuncle and puerperal infection were decreased dramtically by the use of chemotherapeutic agents.

(1) HISTORY OF DRUG RESISTANCE IN BACTERIA

Before the Second World War, more than 100,000 Japanese suffered from bacillary dysentery, and they were isolated from people as an infectious disease defined by the Welfare Department of Japan. This system was convenient for the collection of bacteria and for studies on bacterial serotype and drug resistance. For about 10 years after the use of sulfanilamide(SA), the drug was quite effective against bacillary dysentery as well as infections due to gram-positive cocci such as *Staphylococcus aureus* and *Streptococcus pyogenes*. However there was a rapid increase in the frequency of isolation of SA-resistant *Shigella* strains.

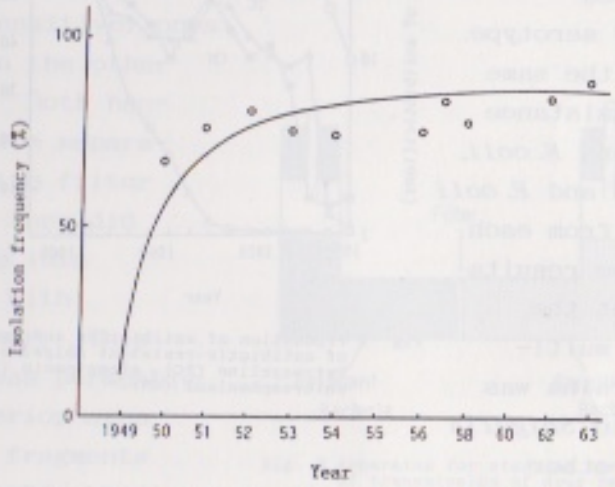

Fig. 1 Isolation frequency of sulfanilamide-resistant *Shigella* strains, survey at various places in Japan. Each point indicates the result for 2000-3000 *Shigella* strains.

After the War, Japan started research and production of chemotherapeutic agents against bacteria. Progress in antibiotics, i.e., penicillin (PC), tetracyclin (TC), streptomycin (SM), chloramphenicol (CM),etc., in addition to sulfonamides (SA) was made in Japan. Production of antibiotics increased rapidly thanks to high level of technology in the fermentation food industries in Japan. Surprisingly, the appearance of antibiotic-resistant *Shigella* strains attracted our attention in Japan (Fig.2).

We were shocked by the isolation, in 1952, a *Shigella* strain resistant to three drugs, i.e., TC, SM, and SA. Three years later, quadruply resistant *Shigella* strains

to TC, CM, SM and SA were isolated. Thereafter, many cases of isolation of multi-resistant *Shigella* strains were reported from many places in Japan.

The spread of multiply resistant *Shigella* strains was concluded no to be due to infectious spread of one strain, because the bacteria showed difference of serotype. In our cases, the same pattern of resistance in *Shigella* and *E. coli*, or *E. freundii* and *E. coli* was isolated from each patient. These results indicated that the isolation of multi-resistant strains was not limited to *Shigella* but included other species of bacteria. The multiple resistance might appear independently and simultaneously in each species of bacteria, i.e. *E. coli*, *E. freundii*, *Shigella*, etc. The isolation frequency of *Shigella* strains resistant to TC, CM and SM increased rapidly and most antibiotics-resistant strains usually carried SA resistance. It was surprising that 79-85% of the antibiotic-resistant *Shigella* strains were resistant to TC, CM, SM and SA. This fact strongly suggests the presence of a big problem in genetics. Ochiai et al. reported the transmission of drug resistance from *Shigella* to *E. coli* strain but questions and discussions were not possible.

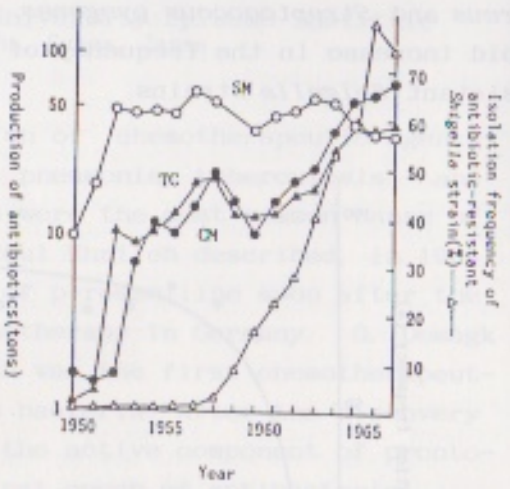

Fig. 2 Production of antibiotics and appearance of antibiotic-resistant *Shigella* strains. Tetracycline (TC), streptomcin (SM) and chloramphenicol (CM).

(2) GENETICS OF BACTERIAL RESISTANCE

At that time, three mechanisms of genetic transfer were known in microbial genetics; transformation by penetraion of DNA into a bacterial cell, (2)transduction of genetic proprties by joining with phage infection and (3)transfer of genetic materials through bacterial conjugation. The bacterial conjugation was quite new finding in USA by Prof. Lederberg. So, we carried out the following experiment to elucidate the mechanism of transfer of drug resistance from bacteria to bacteria (Fig. 3). Drug-resistant bacteria were grown on one side of the culture and recipient (drug sensitive) ones grown on the other side. Both bacteria were separated by the filter so that they did not come into contact with each other. This filter was permeable to bacteriophages and DNA fragments. During a 24 hour incubation period, the culture media were mixed with each other through the filter ten times or so by adding pressure to the bacterial culture or by aspirating it with pump. During this period, the transfer of drug resistance was not observed. However, when the filter was removed and both resistant and sensitive bacteria were mixed, drug resistance was found to be transferred to sensitive ones in a few minutes. Therefore, it was decided that drug resistance was transferred not by DNA fragmentes or bacteriophages, but by conjugation where bacteria came into contact.

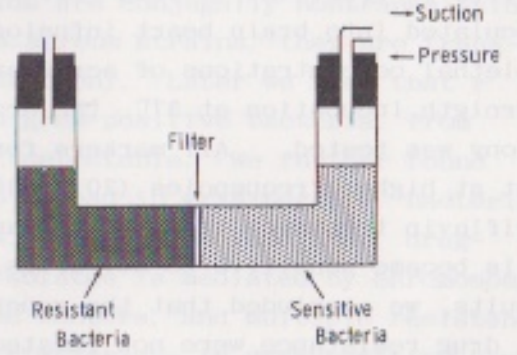

Fig. 3 Apparatus for studying the mechanism of transmission of drug resistance.

We were very interested in multiple resistance in *Shigella* strains, and we collected many strains from various places in Japan. The collected strains were kept in

good condition for a long time. We noticed by chance that multiple (triple or quadruple) resistance was spontaneously lost at a high frequency during storage and the bacteria became drug-sensitve. A single colony of a multiply resistant *Shigella* strain was selected from a cultureplate and maintained in cooked meat medium. After one month of storage in a refrigerator, the culture was spread on an agar plate and the drug resistance of each colony was determined. We found loss of all markers for drug resistance at a high frequency (10 to 20 percent). We also confirmed the elimination of drug resistance by acriflavin treatment. Drug-resistant *Shigella* cells were inoculated into brain heart infusion broth containing sublethal concentrations of acriflavin (10μg/ml). After overnigth incubation at 37℃, the drug-resistance of each colony was tested. All markers for drug-resistance were lost at higher frequencies (20 to 30 percent) due to acriflavin treatment than in spontaneous loss, and the cells became sensitive to all drugs. Based on these results, we concluded that the genetic determinants for all drug resistance were not located on bacterial chromosome but on an extra chromosomal genetic element, termed the "R factor". R factor is a circular double stranded DNA with about 30 μm in length, and composed of genes specifying autonomous replication, conjugal transfer, and drug resistance. Many R factors confer resistance to multiple drugs, such as, four, six, or eight drugs.

Staphylococcus aureus which is a bacteria causative of purulent inflammation, cepticemia, and infection after surgery, has been known to be deeply related with human infectious disease even after chemotherpeutic agents were developed. Majority of *S. aureus* strain were resistant to multiple drugs. Most strains carried bacteriophages, that is, lysogenic. Their drug resistance was not transmissible by conjugation as that of gram negative strain as above mentioned. On the basis of these facts, we started genetical study on *S. aureus* and obtained interesting results. 1. Drug resistance of *S. aureus* is eliminated from the host strain. The drug resistance factor is smaller than R factor and nontransmissible by conjugation. We designated this small resistance factor as r factor to distinguish from R factor. It is usual for r factors to confer resistance to single or double drug(s) but not to multiple drugs. The most distinct difference from R factor is that r factors have no genes for conjugal transfer, as being expected by the small size of about 1/10 of R factors. Then the multiple drug resistance in *S. aureus* is conferred by many kinds of resident r plasmids in a cell. Althoug r plasmids are conjugally nontransmissible by conjugation between *S. aureus* strains, they are transferred by phages (transduction). Later we knew that r factors spread widely in gram-positive bacteria, from which R factors were not detectable. We further found that r factors were also spread in gram-negativ bacteria, which harbored R factors. We can conclude that drug-resistance of clinical isolates is mediated by chromosomal genes and drug-resistance factors, and multiple resistance is conferred by(1)r, (2)r1+r2+r3--- in gram-positive bacteria and by (3)R, (4)R1+R2, (5)R+r in gram-negative bacteria. In the case of broiler, cattle, or culture fish, which are supplied with many kinds of drugs to prevent bacterial infection, many isolates of bacteria are resistant to multiple drugs and harbor resistance factors as seen in isolates from human focus of infection.

During detailed analysis of R factor conferring four drugs, R(TC.CM.SM.SA) by transduction experiment with a phage P1, we happened to isolate a P1-CM, in which chloramphenicol resistance gene of the R factor had translocated onto the phage P1 by transposition. As the phage P1-CM is an active phage carrying CM resistance gene, lysogenization after infection of P1-CM confers CM resistance on the host bacteria. Infection of P1-CM to bacteria which harbored F factor or R factor as the resident

plasmid results in formation of F-CM or R-CM. The gene CM on PI-CM is easily transposable to the host chromosome. We further found during transducion experiment using a phage ε that TC resistance gene of R(TC.CM.SM.SA) transposed to the host chromosome. The TC resistance gene was easily transposable again from chromosome to F factor, resulting information of F-TC or R-TC. The phenomenon we first found was so intersting that the international symposium was held at Cold Spring Harbor in United States of America in 1977. The phenomenon of transposition of drug resistance genes from R factor to phages or chromosome was accepted with great interest. The gene was called as "jumping gene" and named transposon in the congress.

(3) BIOCHEMICAL MECHANISMS OF DRUG RESISTANCE

(1) Aminoglycoside antibiotics. In 1965, Okamoto and Suzuki found the presence of enzyme that catalyzed the reaction of kanamycin A with acetylCoA. After that Umezawa et al. studied a strain which was resistant to kanamycins, and found that the enzyme of this strain transfers the phosphate group of adenosine triphosphate to the 3′-hydroxyl group of kanamycins. Similar phosphotransferases were widely distributed among resistant bacteria and were found also in resistant Staphylococci and *Pseudomonas aeruginosa*. Aminoglycoside antibiotics are inactivated by phosphorylyation or adenylylation of hydroxyl groups of the drugs in the presence of ATP. They are also inactivated by acetylation of their aminogroups in the presence of acetylCoA. In that time, Mitsuhashi was asked to propose a rational nomenclature for the phenotype of aminoglycoside antibiotic reistance. He proposed the following nomenclature and abbreviations for the inactivating enzymes, such as aminoglycoside phosphotransferase(APH), aminoglycoside acetlytransferase(AAC) and aminoglycoside adenylyltransferase(AAD), from the substrate profiles or resistance patterns.

(2) β-Lactam Antibiotics. β-Lactamase was found to be the main factor for the β-lactam resistance. β-Lactamase is an enzyme which hydrolyzes the C-N bound in the β-lactam ring of penicillins causing irreversible inactivation. In general β-Lactamases are classified into two groups according to their substrate profiles, i,e., penicillinases and cephalosporinases. Penicillinases prefer penicillin to cephalosporin substrates. Genetic and epidemiological studies have disclosed that the genes governing the formation of penicillinases are mostly located on plasmid or are mediated by transposons. However, cephalosporinase producing genes are located in the bacterial chromosome and their substrate profiles are almost the same in each organism belonging to the same species. All these β-lactamases are grouped in details by substrate profiles, inhibition pofiles and immunological properties. During these studies, we found that the new β-lactamase producedby *Proteus vulgaris*, *Bacteroides fragillis* and *X. maltophilia* had a unique substrate profile and hydrolyzed the new cephalosporins, so called third generation cephems. The enzymes produced by these organisms are called oxyiminocephalosporinase(CXase).

(3) Chloramphenicol. The chloramphenicol inactivating enzyme, called chloramphenicol acetyltaransferase(CATase) was detected in chloramphenicol-resistant strains of *S. aureus* and inactivated chlormphenicol in the presence of acetylCoA. It was quite similar to that from the plasmids meidated resistant strains in its enzymological properties. During these studies, we found that chloramphenicol resistant gene(*cmI*) was integrated on the different sites of chromosome and *cmI* gene was translocated from chromosome to plasmid. On the contrary, chloramphenicol acetyltransferase from an R plasmid isolated from *Vibrio anguillarum* was different from that of the human and animal origins by enzymological and immunological properties. The chloramphenicol acetyl-

transferase derived from *V. anguillarum* chloramphenicol-resistant plasmid is a new type of chloramphenicol acetyltransferase mediated by plasmids of gram-negative bacteria.

(4) IMPORTANCE OF R PLASMIDS IN MEDICAL FIELDS

It was under the conditions that conjugative and non-conjugative resistance plasmids were discovered in Japan, and we then realized the reason for the rapid spread of multiply resistant strains in hospitals, livestock farming, and the fish breeding industry. Knowledge of the existence of plasmids and transposons has broadened our perspective on the role of genetic exchanges and gene spread in the revolutionary changes in bacterial species in response to enviromental circumstances. Drug resistance plasmids have caused many problems in medicine and pharma-ceutical science. The traditional approach to the ongoing problem of antimicrobial drug resistance in bacteria has been to develop increasingly modifying and hydrolysing enzymes stable drugs, such as the broad-spectrum and extended-spectrum agents. These newer antimicrobial agents are clearly superior to their protype drugs, but resistance has continued to be problematic. At the same time, however, drug resistances have brought about the development of a new plasmids that will yield the endeavors to the benefits in many aereas of human beings.

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Symposia

Chairman's Introduction

Chairman: Jan E. Veldman, M.D.,Ph.D.
Utrecht, The Netherlands

Co-chairman: Goro Mogi, M.D.
Oita, Japan

The lining of the upper-respiration tract, including Eustachian tube and middle ear-mastoid complex presents a formidable physical and chemical barrier to infective organisms and represents a first line of defence. It provides a natural barrier system towards infection but is, unfortunately, often less than perfect.

Microorganisms have evolved in such a way that they resist destruction or physical removal and penetrate the body's lining, particularly at the site of an injury.

Defects may exist at the level of this first line of defence.

In this symposium recent data are presented on ciliary function analyses in the nose (K. Ingels) and bacterial adherence problems (D. Lim). After an "injury" of the mucosal lining, cells of the immune system come into play: they recognize the invading agents and make an immune reaction against them which either neutralizes and destroys and/or makes the host hyperreactive, allergic for the agent. New data on the cellular components of our second line of defence system in the nose and middle ear are presented (W. Fokkens; H. Kawauchi).

Homing of lymphoid cells towards the nose and middle ear - mastoid complex mucosal lining follows apparently specific rules. As in the skin Langerhans cells fulfill the same custodian role in the mucosa of allergic individuals.

Both antigen presentation as well as effector site phenomena seem to be dependent on the Langerhans-T-cell repertoire, also at the mucosal level.

Immunochemical aspects of mucosal immunity of the nose

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INTRODUCTION

Nasal mucosa is considered to be the first defense line of the respiratory tract, protecting it from invading antigens. The local immunity of the nose has been well investigated and mucosal immunity has been proven to be present in nasal mucosa as well as bronchial and intestinal mucosae(Nakashima et al,1980). An established immunohistochemical technique with available monoclonal antibodies has been accelerating precise analyses of immunocytes recruitment at these mucosal sites. To better understand the role of nasal mucosa in the defense mechanism of the upper respiratory tract, we conducted following experiments as shown below.

1. The distribution pattern of lymphocyte subsets was investigated in normal nasal mucosa of mice fed in three different conditions; germ-free(GF), specific pathogen-free(SPF), and conventional(CV) conditions.

2. To see effects of viral infection in nasal mucosa on the local and systemic immune response upon the antigenic exposure to the nasal cavity, IgG and IgA antibody titers were examined in sera, nasal washings and lung lavage fluids at each interval after antigen introduction to the nasal cavity.

MATERIALS AND METHODS

I. DISTRIBUTION OF IMMUNOCOMPETENT CELLS IN NASAL MUCOSA

ANIMALS

Strain ICR male mice 6 to 8 weeks old were used for the experiments. A total of 15 ICR mice(5 each) were purchased in GF, SPF, and CV conditions and confirmed to be free of infection in the nasal cavity.

TISSUE PROCESSING AND IMMUNOSTAINING

Briefly described, nasal mucosae were fixed with periodate-lysine-paraformaldehyde(PLP), then decalcified with 10 % ethylenediaminetetraacetic acid(EDTA) in Tris buffer(pH 6.95), embedded in OCT compound, and sectioned at 6-μm thickness vertically to the long axis of the nasal cavity. Thereafter, serial sections were stained by an indirect immunoperoxidase method, employing available antibodies.

HISTOLOGIC EVALUATION

Positive cells in nasal mucosa that were stained by the

immunoperoxidase technique were observed by light microscopy. For quantitative analysis, cell counting was done in each specimen at the same portion of the nasal cavity. The portion was the coronal section at about the anterior one third of the nasal cavity. Details of the quantitative study were described in a previous report(Ichimiya et al, 1990).

II. EFFECTS OF VIRAL INFECTION IN NASAL CAVITY ON THE LOCAL AND SYSTEMIC IMMUNE RESPONSE UPON ANTIGENIC EXPOSURE TO THE NASAL CAVITY

ANIMALS

Strain Balb/c male mice 6 weeks old,bred in SPF condition were used for experiments.

VIRUS

Type A influenza virus(H3N2) was obtained from Dr. Mifune (Virology Department, this college), propagated in allantoic sacs of 10-day-old embryonated chicken eggs, and stored at -70°C as infectious allantoic fluid.

EXPERIMENTAL PROTOCOLS

Balb/c mice were intranasally challenged with 100 hemoaggulutination(HA) unit/25 µl of type A influenza virus. Seven days post virus challenge, 100 ug of ovalbumin(OVA) distilled in 2 µl of sterile phosphate buffered saline(PBS) or 0.8 % hydroxypropyl cellulose (HPC) solution was introduced into the nasal cavity. HPC solution was used to ensure antigen contact with nasal mucosa. The viral infection of the nose and lung was confirmed by histology and recovery of virus from nasal washings and lung tissue homogenate at 7 days post virus challenge. After the intranasal immunization of OVA, the IgG and IgA antibody titers were monitored in sera, nasal washings, and lung lavage fluids at 1, 2, 3, and 4 weeks post intranasal OVA challenge. The sampling of nasal washings was carried out by washing the nasal cavity with 200 µl of PBS with 26 gauge needle and syringe. Lung lavage fluids were also obtained by washing trachea with 200 ul of PBS.

ANTIBODY TITRATION

Antibody titration was performed by an enzyme-linked immunosorbent assay(ELISA), employing peroxidase-conjugated goat anti-mouse IgG and IgA antisera.

RESULTS

I. DISTRIBUTION OF IMMUNOCOMPETENT CELLS IN NASAL MUCOSA.

In the nasal mucosa of all mice bred in GF, SPF, and CV conditions, lymphocytes were dominant, even though neutrophils and macrophages were also present. However, the numbers of lymphocyte subsets were different among the three conditions(Table 1). In the nasal mucosa of CV mice, B-cells(IgG, IgM, and IgA-bearing), Lyt-1+ T ,

and Lyt-2+ T cells were abundant, while these cells were fewer in SPF mice. In the nasal mucosa of GF mice, a small number of lymphocytes, Mac-1+ cells were seen. As for the lymphocyte subset, only IgM+ cells and Lyt-1+ cells were seen. Neither IgG+ cells nor IgA+ cells were seen. A small number of Lyt-2+ cells were seen in two animals out of five, which was exceptional. Interestingly, follicle-like lymphocyte aggregates with high endothelial venules was present in the nasal mucosa close to mucosal epithelia on the floor of the nasal cavity. Lymphocyte aggregates of CV mice in size was much larger than those of SPF or GF mice.

II. EFFECTS OF VIRAL INFECTION IN NASAL MUCOSA ON THE IMMUNE RESPONSE UPON ANTIGENIC EXPOSURE TO NOSE

OVA-specific IgG and IgA antibody titers in sera, nasal washings, and lung lavage fluids of control(virus non-infected) and virus-infected mice were monitored at 1, 2, 3, and 4 weeks after the intranasal administration of 100 µg of OVA distilled in PBS or HPC solution. As shown in Figure 1, in virus-infected mice, a considerable amount of OVA-specific IgG antibody was detected in sera at 3 or 4 weeks after the intranasal immunization. But no IgG antibody was detected in control mice throughout experimental period. In nasal washings and lung lavage fluids of virus-infected mice, elevation of OVA-specific IgG antibody was seen from 2 weeks to 4 weeks after the intranasal immunization, but no IgG antibody response was seen in control mice. As for IgA response, a slight elevation of OVA-specific IgA antibody titer was seen at 4 weeks after the intranasal administration of 100 ug of OVA in sera of virus-infected mice,while no IgA response was seen in sera of control mice. On the other hand, in nasal washings and lung lavage fluids, OVA-specific IgA antibody titer was elevated upto 2^5 at 3 weeks post intranasal administration of OVA in virus-infected mice, while no IgA antibody was detected in control mice.

DISCUSSION

The comparative study of immunocompetent cells in nasal mucosa of mice bred in different conditions showed that there were fewer immunocompetent cells in GF mice than in SPF and CV mice. And the number of lymphocytes in nasal mucosa per unit area was much higher than that of middle ear mucosa, which is exposed to less antigenic stimuli(Ichimiya et al,1991). Moreover, follicle-like lymphocyte aggregates was seen in the subepithelial layer on the floor of nasal cavity with a different size among GF, SPF, and CV mice. These results taken together suggest that nasal mucosa can mature in its immunocompetence by repeated environmental antigenic stimuli, and also suggest the possibility that immunoglobulin forming cells in the nasal mucosa are locally

differentiated from the lymphocyte aggregates upon the antigenic invasion to the nasal cavity. In another study, we examined the effect of the viral infection of the nasal cavity on the systemic and local antibody response to OVA administered intranasally. The data presented herein demonstrated that type A influenza virus infection in the upper respiratory tract augmented systemic and local antibody(IgG/IgA) response to OVA introduced into the nasal cavity. The mechanism of this effect is not known yet, but antigen uptake from the nose to systemic circulation was proven to be increased in our study with ^{125}I-labelled OVA and the in vitro proliferative response of spleen cells to OVA in virus-infected mice indicated that the mice were systemically sensitized after the intranasal immunization of 100 μg of OVA (data not shown). These results might suggest that viral infection in the upper respiratory tract accelerates antigen uptake from the nose to systemic circulation and augment the systemic and local immune response. However, especially in regard to IgA response in virus-infected mice, no conclusive data is obtained whether local IgA production is the case or not in this experiments. Therefore, further precise studies will be required to clarify the effects of viral infection on the immune response of the nose.

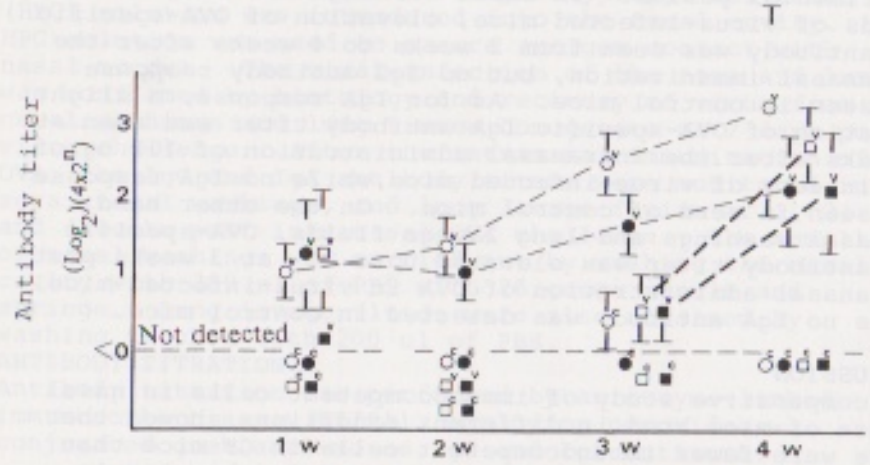

Fig.1, OVA-specific IgG and IgA antibody titers in sera after the intranasal OVA challenge.

○ ; IgG Ab titer OVA/PBS.
● ; IgG Ab titer OVA/HPC.
□ ; IgA Ab titer OVA/PBS.
■ ; IgA Ab titer OVA/HPC.

V: virus-infected mice
C: control mice

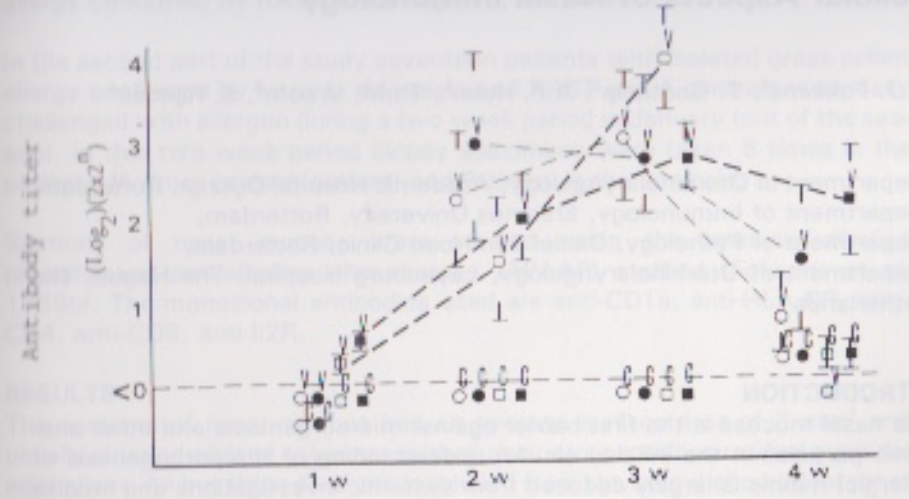

Fig 2. OVA-specific IgG and IgA antibody titers in nasal washings after the intranasal OVA challenge.

;IgG Ab titers, OVA/PBS.
;IgG Ab titers, OVA/HPC.
;IgA Ab titers, OVA/PBS.
;IgA Ab titers, OVA/HPC.

V: virus-infected mice
C: control mice

Table 1. Distribution of immunocompetent cells in nasal mucosa

Lymphocyte subset	GF	SPF	CV
IgG+ cells	0.0(0.0- 0.0)*	16.6(0.0- 70.8)	721.7(237.7- 868.6)
IgA+ cells	0.0(0.0- 0.0)	73.8(35.9- 118.0)	399.3(160.0- 502.2)
IgM+ cells	45.5(0.0-121.9)	27.9(17.5- 88.6)	127.6(13.1- 418.9)
Lyt-1+ cells	108.1(0.0-185.7)	400.0(73.4-1070.0)	1749.8(1006.1-2043.0)
Lyt-2+ cells	0.0(0.0- 23.0)	53.1(21.7- 554.2)	640.8(277.8-1263.5)
Mac-1+ cells	30.9(0.0- 42.1)	70.7(7.1- 149.0)	442.9(266.2- 569.0)

* Data are cells/mm^2, median(range); N=5 for each sample tested

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Cellular Aspects of Nasal Immunology

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INTRODUCTION

The nasal mucosa is the first barrier against microorganisms and other antigenic particles in the inhaled air. An understanding of the pathogenesis of (allergic) rhinitis is largely deduced from systemic investigations and studies in the skin and the lung. Studies on rhinitis generally comprise clinical aspects and/or biochemical, humoral and cellular features of the epithelial surface and the nasal secretions. Little was known about what happens in he nasal mucosa itself.

In recent years a biopsy method was developed which made it possible to obtain high-quality specimens of nasal mucosa in a patient friendly way (Fokkens et al. 1988). Lately various research groups used immunohistochemical staining techniques to identify and quantify the cell populations occurring in nasal mucosa with the use of monoclonal antibodies against surface antigens (Nishimoto et al. 1988, Stoop et al. 1989, Fokkens et al. 1989a, Fokkens et al. 1990a).

In this manuscript the results of studies concerning the pathogenesis of allergic rhinitis with special emphasis on antigen presenting cells like Langerhans cells are discussed.

MATERIALS AND METHODS

Biopsies were taken from the lower edge of the inferior turbinate with a specially designed forceps, the Gerritsma forceps after local anaesthesia with cocaine (Fokkens et al. 1988).
The specimens were embedded in Tissue-Tek II O.C.T. compound in a gelatin capsule and frozen immediately.

In the first part of the study in 12 patients with isolated grass pollen allergy confirmed by history, skin tests and RAST (mean age 30, 4♂, 8♀) nasal biopsies were performed four times in each patient, i.e., in July during the grass pollen season, in October and March and in July of the following year. Biopsies were also taken in 12 controls without nasal complaints, no abnormalities in the nose seen at ENT-examination and no allergy confirmed by RAST (mean age 28, 3♂, 9♀) and 11 patients with nasal polyps and no

allergy confirmed by RAST (mean age 36, 7♂, 4♀).

In the second part of the study seventeen patients with isolated grass pollen allergy confirmed by history, skin tests and RAST and 4 controls were daily challenged with allergen during a two week period in January (out of the season). In this two week period biopsy specimens were taken 8 times in the patients (4 times in each patient) and 3 times in the controls.

Sections of nasal mucosa were stained using the immuno alkaline phosphatase anti-alkaline phosphatase (APAAP) method (Fokkens et al. 1989b). The monoclonal antibodies used are anti-CD1a, anti-HLA-DR, anti-CD4, anti-CD8, anti-Il2R.

RESULTS

The sections of nasal mucosa had an average surface area of 3 mm^2 and usually showed ciliated columnar epithelium and/or partially stratified cuboidal epithelium. All but three sections (excluded from the study) showed intact or virtually intact epithelium.

All but three sections showed $CD1a^+$ dendritic cells, presumably Langerhans cells, in the middle and lower layers of the epithelium and all sections showed $CD1a^+$ dendritic cells in the lamina propria predominantly in the

Table 1. **Numbers of $CD1a^+$ cells/mm^2 in epithelium and lamina propria of nasal mucosa in patients with isolated grass-pollen allergy, patients without nasal complaints, and patients with nasal and/or sinusal polyps.**

Group	Patients (n = 35)	$CD1a^+$ cells	
		Epithelium	Lamina propria
		Mean (SD)	Mean (SD)
I	with grass-pollen allergy (n = 11) *	55 (49.5)	14 (22.0)
II	without nasal complaints (n = 12)	20 (14.1)	4 (4.0)
III	with nasal and/or sinusal polyps (n = 12)	28 (23.1)	10 (10.4)
Kruskal-Wallis overall p-value#:		0.047	0.046
Mann-Whitney: p-value I vs. II/III#		0.018	0.224
p-value II vs. I/III#		0.74	0.013

* In one of these patients the epithelium was damaged; this epithelium was not included in the study.
\# A difference between two patient groups was accepted as significant when the p-value was < 0.05.

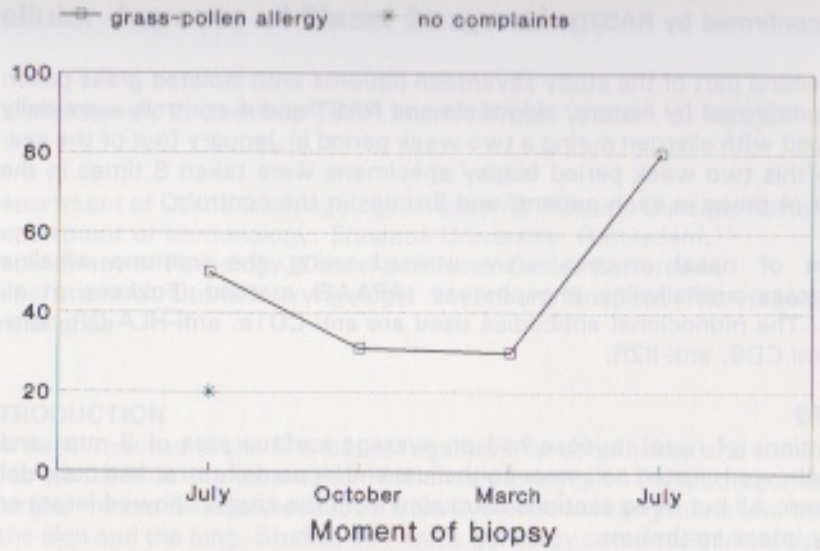

Fig.1 CD1a⁺ cells/mm² in the epithelium and the lamina propria of the nasal mucosa in 12 patients with an isolated grass-pollen allergy before, during, and after the grass-pollen season and 11 controls.

subepithelial layer and in and around the glandular tissue.
The CD1a⁺ Langerhans cells (LC) were found to be significantly more numerous in nasal biopsy samples of patients with isolated grass pollen allergy than in non-allergic controls without complaints or non-allergic patients with nasal polyps (Table 1). In the allergic patients 20-40% of the CD1a⁺ was positive for IgE.

To find out whether the number of CD1a⁺ LC in the nasal mucosa of patients with isolated grass pollen allergy depends on the season in which the nasal biopsy is performed, nasal biopsies were performed four times in each patient, i.e., in July during the grass pollen season, in October and March and in July of the following year. During the grass-pollen season the nasal epithelium of patients with an isolated grass-pollen allergy showed significantly more CD1a⁺ cells than it did before and after the season.
Before and after the season, the number of CD1a⁺ cells in epithelium of the allergic patients was not significantly greater than the corresponding number in epithelium of non-allergic subjects without nasal complaints (Fig. 1).

To further study the dynamics of LC in allergic rhinitis, a provocation study was performed in 17 patients with an isolated grass-pollen allergy during 2 weeks in January. The study showed that the number of LC increased significantly in the epithelium and the lamina propria of these patients. Significantly, already in the acute phase, ½ hour after the first provocation, a threefold increase in LC numbers was seen in the epithelium. The increase in the lamina propria occurred later, approximately 24 hours after the first provocation (Fig. 2).

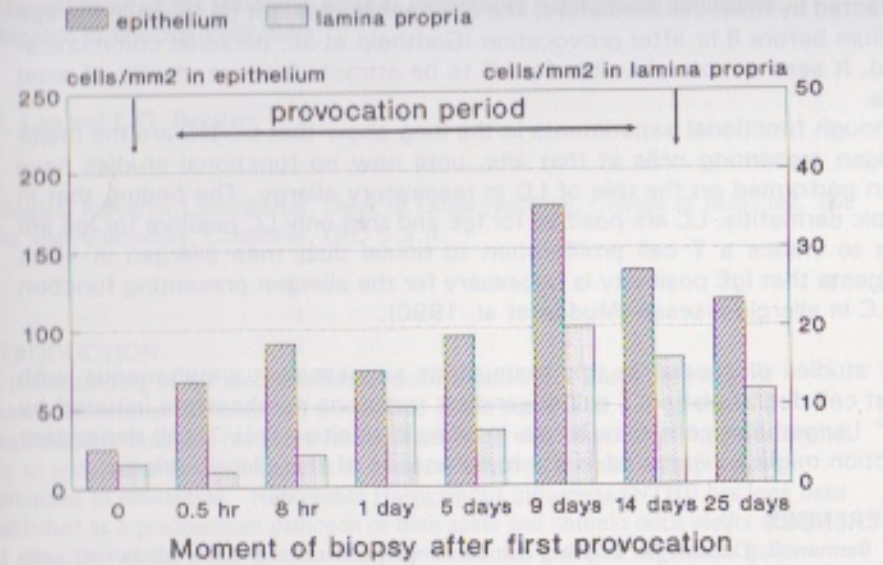

Fig. 2 Median number of CD1a⁺ cells in the epithelium and the lamina propria of the nasal mucosa of patients with an isolated grass-pollen allergy before, during, and after a two-week provocation study. A significant increase in CD1a⁺ cells was found in the epithelium and the lamina propria during the provocation study.

DISCUSSION

The aim of the investigations discussed in this manuscript was to study the pathogenesis of allergic rhinitis with special emphasis on allergen presentation, using immunohistochemical staining techniques on biopsy specimens of nasal mucosa.

Langerhans cells (LC) are capable of binding and presenting potentially antigenic molecules to T lymphocytes and probably to other cells as well. Furthermore, LC are able to secrete immunoregulatory factors, for example, interleukin-1 (Sauder et al. 1984), interferon-gamma (Enk et al., 1987), prostaglandin D2 (Berman et al., 1988) and IgE binding factors (Bierber, 1990). By virtue of these capabilities, LC play a role in atopic disease (Fokkens 1990b).
In respiratory allergy, part of the LC are positive for IgE. The number of LC is larger in patients with allergic rhinitis than in non-allergic controls. In such patients the number of LC is higher during natural allergen provocation than without allergen provocation. Also during allergen provocation studies the number of LC increased significantly in epithelium and lamina propria during the provocation period. The increase in the provocation study is larger than that found during natural provocation, probably due to the strong allergen stimulus continuing on a daily basis.
The mechanism which attracts LC to the epithelium is not exactly clear. The finding that LC increase already within half an hour after provocation makes it unlikely that LC are attracted by mast cell mediators. Other cells which are

attracted by mast cell mediators, like eosinophils, can not be found in the epithelium before 8 hr after provocation (Godthelp et al., personal communication). It seems more plausible for LC to be attracted independently of mast cells.
Although functional experiments in the lung show that LC/DC are the major antigen presenting cells at that site, until now no functional studies have been performed on the role of LC in respiratory allergy. The finding that in atopic dermatitis, LC are positive for IgE and that only LC positive for IgE are able to induce a T cell proliferation to house dust mite allergen in vitro, suggests that IgE positivity is necessary for the allergen presenting function of LC in allergic disease (Mudde et al. 1990).

The studies discussed in this manuscript suggest that simultaneous with mast cell degranulation T cell dependent reactions mechanisms initiated by IgE^+ Langerhans cells play a role in allergic rhinitis. This T cell dependent reaction might be involved in the maintenance of the allergic rhinitis.

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An Investigation of the Molecular Basis of Nontypable Haemophilus influenzae Adherence to Mucosal Epithelium.

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INTRODUCTION

An understanding of the mechanisms of bacterial adherence and a definition of adhesive molecules (adhesins) on the surface of the bacteria as well as the complimentary host cell receptors for those adhesins will afford a new opportunity not only to understand the pathogenesis of mucosal infection but also to apply new approaches to prevention. Nontypable Haemophilus influenzae (NTHi) has long been established as a predominant pathogen of both acute and chronic otitis media (OM) and sinusitis, yet the exact mechanism(s) by which this group of organisms gains access to the tubotympanum or sinuses, colonizes the mucosal epithelium and later induces disease is not known. Neither is the nature of the host's immune response to this heterogeneous group of organisms fully understood.

Newly characterized fimbriae have been found on all clinical isolates of NTHi recovered from cases of chronic OM examined to date (5). This fimbrial appendage has been demonstrated to be both morphologically and functionally distinct from the classically described pilus of type b H. influenzae (Hib), which is believed to be involved in bacterial adherence. While there is evidence that NTHi fimbriae are involved in adherence of this group of bacteria to human epithelial cells, there is, as yet, no data available to indicate that they are a virulence factor. Our laboratories have undertaken a series of studies over the past five years to define and characterize the role that these fimbriae play in the development of OM and determine the immunological significance of these structures. We are actively investigating whether or not the subunit of these fimbriae might be considered as a viable candidate for inclusion in a component vaccine aimed at the prevention of OM and possibly sinusitis. These collective data will be presented.

MATERIALS AND METHODS

Preparation of negative stains and specimens for light and electron microscopic observation and protocols used for inoculation of chinchillas as models of experimental OM can be found in several published papers and abstracts (1-5). A complete listing of methodologies is too extensive for inclusion within the page limitations indicated for publication in this format, but some critical ones are included under each heading.

RESULTS

1. Frequency of Fimbriation of NTHi Isolates Recovered from Cases of Chronic OM.

We have found that 100% of those isolates examined bore a filamentous surface appendage which we have referred to as "fimbriae" (5). These structures were found to be morphologically and functionally distinct from the "pili" classically described for Hib isolates in that fimbriae were narrower, lacked both a hollow core and the characteristic helical appearance of pili and additionally were not associated with hemagglutination. The former, by transmission electron microscopic observation, appear to be involved in adherence of NTHi to human oropharyngeal (OP) cells (5). Interestingly, these finer, more filamentous fimbriae have recently been demonstrated on several Hib isolates which also express classic pili under certain conditions (8). Many of these Hib strains were recovered from the blood of patients with systemic disease, and had been considered to be non-appendage producing due to a lack of pili. Clearly it is now important to reconsider some of the previously accepted generalizations which have been made about how these organisms behave once they reach the blood or CSF. The local host environment may induce selective pressures which in turn affect which or how many surface appendages an organism produces and may have important ramifications when considering OM as well.

2. Inhibition of Adherence of NTHi to Human OP Cells.

One standard method used to begin characterization of the bacterial adhesin(s) (often fimbriae or pili or specific components of the glycocalyx) and host cell receptor(s) (typically a glycoprotein or glycolipid present on the cell surface) involved in the interrelationship between the prokaryote and eukaryote is to attempt to inhibit this binding. This is done by pre-incubation of either cell type with various potential host receptor components (for bacterial pre-incubation) or isolated bacterial adhesins (for eukaryotic cell pre-incubation) or their analogues. Typically an inhibition pattern will emerge which will indicate those moieties which are most likely involved in the adherence. We have performed these studies using our prototype NTHi strain and human OP cells by both direct microscopic count (DMC) and an adherence ELISA technique. Of the numerous agents tested, via both pretreatment of either bacterial or OP cells, those which either contained sialic acid moieties or bound to or destroyed these residues were the most effective in inhibiting adherence of NTHi whereas others were either marginally or non-inhibitory (1). Isolated fimbrial subunits but not an additional unrelated outer membrane protein inhibited binding in a dose-dependent fashion as well (1).

3. Isolation of a Pilin-Like Gene from NTHi #1128 and Evidence to Support the Lack of Identity between Pilin and Fimbrin Subunits.

We have used oligonucleotide primers based on the published nucleotide sequence of Hib strain Eagan (9) and PCR to isolate clone and sequence a pilin-like gene from the genome of NTHi strain #1128. The open reading frame (621 b.p.) demonstrated significant homology (64-69%) to that of several type b and another nontypable strain (Fig. 1) (7,10-12). Partial amino acid sequencing of a fragment of the isolated fimbrial monomer and Western blot data has indicated however that the cloned gene does not encode for the observed NTHi fimbriae and that these two structural subunits appear to be immunologically distinct. These findings are significant because there has been considerable debate concerning the distinction between fimbriae and pili. While data has amassed to indicate that these two are structurally and functionally distinct, the unresolved issue has been whether or not they are comprised of identical subunits which are either assembled differently or with additional accessory proteins, tip adhesins, etc. which might account for these distinctions. Our preliminary data

would indicate that this is not the case. The ability of these bacteria to express two distinct structures that might possibly serve very different functions is indeed intriguing.

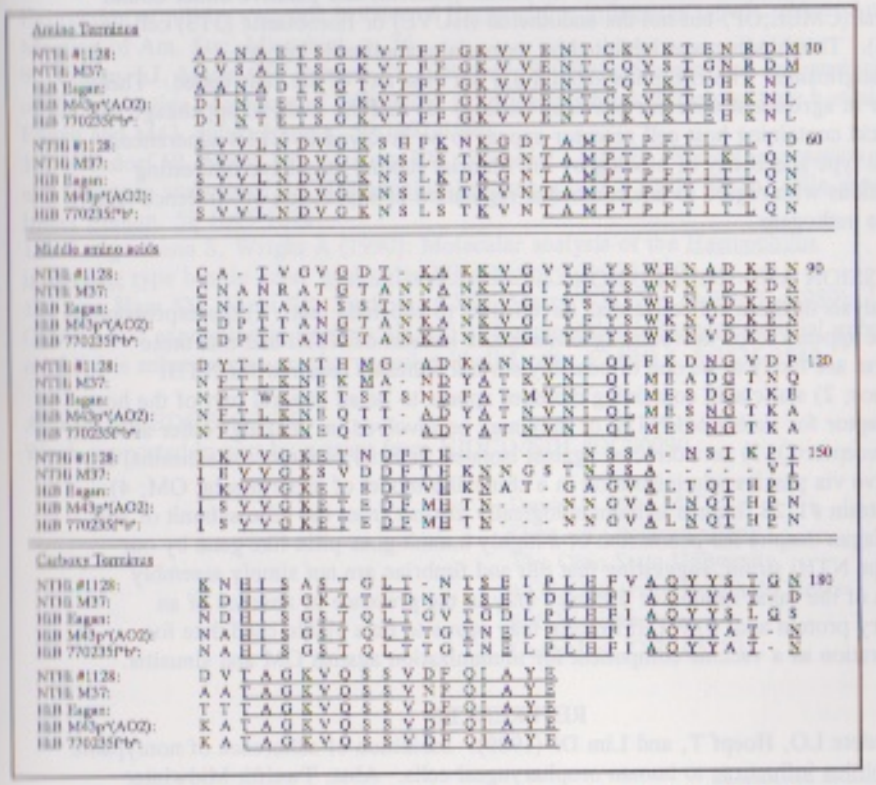

Fig. 1: Comparative analysis of the translated amino acids of NTHi #1128 fimbrin with those of pilin-like subunit with those of pilin from several HiB and one NTHi strain. Underline indicates identical or functionally identical residues as compared with NTHi #1128. (Ser and thr and phe, trp and tyr were assumed to be functionally identical.) Dashes indicate gaps introduced to optimize homology.

4. Protection of Chinchillas Against Experimental OM via Passive Immunization with Anti-Fimbrin Sera.

Chinchillas immunized via intracardiac injection of either rabbit or chinchilla anti-fimbrin sera and challenged 24 hours later by intrabullar injection of viable homologous fimbriated NTHi were shown to have a greatly reduced incidence of middle ear fluids (MEF) (2) and a significant ($p \leq 0.001$) reduction in tympanic membrane pathology when compared to controls. These data indicate that anti-fimbrin antibodies could temper or interrupt the natural disease process involved in OM.

5. Presumptive Characterization of the NTHi Adhesin for Chinchilla Middle Ear Epithelial (CMEE) and Human OP Cells.

Using a newly adapted modification of a Western blot (6) in which eukaryotic cells were allowed to bind to the bacterial outer membrane protein (OMP) of interest once separated by PAGE, we have characterize those bacterial OMPs which may be involved in adherence. The fimbrial monomer (fimbrin) and putative dimer bound epithelial (CMEE;OP) but not the endothelial (HUVE) or fibroblastic (3T3) cell lines used (3). This binding was inhibited by monosialoganglioside but not asialoganglioside. The Hib pilus subunit did not bind any of the cells tested. These data are in agreement with our previous findings (1) that the fimbrial appendage and a sialic acid containing host cell receptor appear to be involved in NTHi adherence. The cell type specificity of binding by the fimbrial subunit may have interesting implications with regard to environmental regulation of expression of virulence factors by these pathogens.

DISCUSSION AND CONCLUSION

The analysis of these collective data have led us to conclude that: 1) the expression of fimbriae appears to be universal by otitis media isolates of NTHi and that these structures are likely to be one of possibly several adhesins required for NTHi adherence; 2) sialic acid containing moieties appear to be an integral part of the host cell receptor for fimbriated NTHi or they may be involved in "locking" other adhesins to the receptor(s); 3) sera directed against isolated fimbrial subunits (or adhesins) are protective via passive administration in a chinchilla model of experimental OM; 4) NTHi strain #1128 fimbrin is immunologically distinct from the pilin subunit of Hib strain Eagan despite the possession of a highly homologous pilin-like gene by our prototype NTHi strain, suggesting that pili and fimbriae are not simply assembly variants of the same subunit or different only in the presence or absence of an accessory protein and; 5) NTHi fimbrin may prove to be a viable candidate for consideration as a vaccine component for immunization against OM and sinusitis.

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Ciliary Beat Harmony another Parameter for Ciliary Function

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INTRODUCTION

Ciliated epithelium is very important in the defense system of the upper airways. The photoelectrical method is a well accepted technique to record ciliary movements [1]. The photoelectrical signal has a complex waveform and is analyzed in an objective way by Fourier transform [3]. Up till now ciliary beat frequency (CBF) has been used as the only measure for ciliary function.

MATERIALS AND METHODS

The movements of normal nasal cilia were recorded photoelectrically in six subjects. A power spectrum was made of the signal in order to measure CBF. An average 0.2-sec period was computed; the average standard deviation (ASD) served as a measure for the non-uniformity of the signal. We introduced another parameter, signal consistency (SC), which is defined as

$$SC = 1/ASD \times 100.$$

Both parameters were investigated under three conditions:
1) normal or "initial", 2) after induction of "function loss", and 3) after "salbutamol stimulation" [2].

RESULTS

In the "function loss" condition the cilia were beating slower and with diminished harmony. CBF decreased from an average of 9.0 Hz in the "initial" condition to 5.8 Hz (Fig. 1). SC decreased from an average of 5.7 to 1.9 (Fig. 2). After "salbutamol stimulation", average CBF was partially restored to 7.7 Hz, while average SC was restored to 4.4 Hz.

DISCUSSION

These findings indicate that in the study of ciliary function, apart from CBF, SC may be used as a second valuable parameter, more in particular as a measure for ciliary beat harmony. It should be of great clinical and scientific importance in the future to correlate these findings with the effectiveness of the mucociliary transport in the nose. We advocate the use of SC in pharmacological studies on ciliary movement.

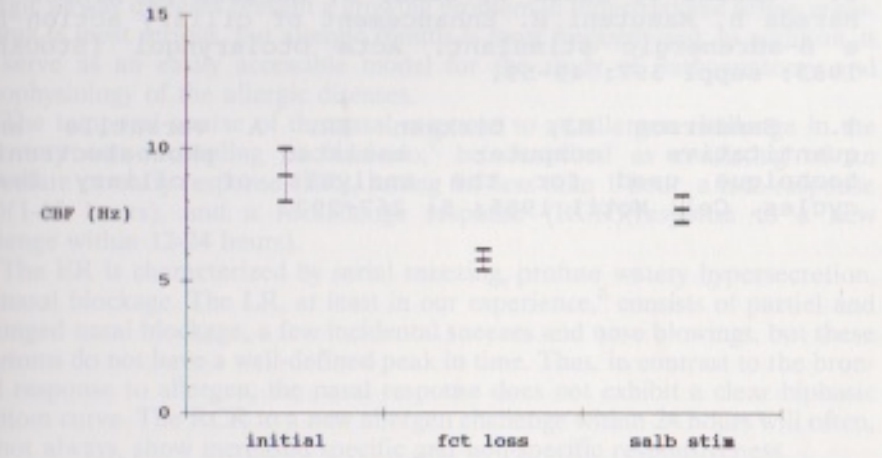

Fig. 1 Average ciliary beat frequency (CBF) with standard deviation of the "initial," "function loss," and "salbutamol stimulation" condition (six subjects).

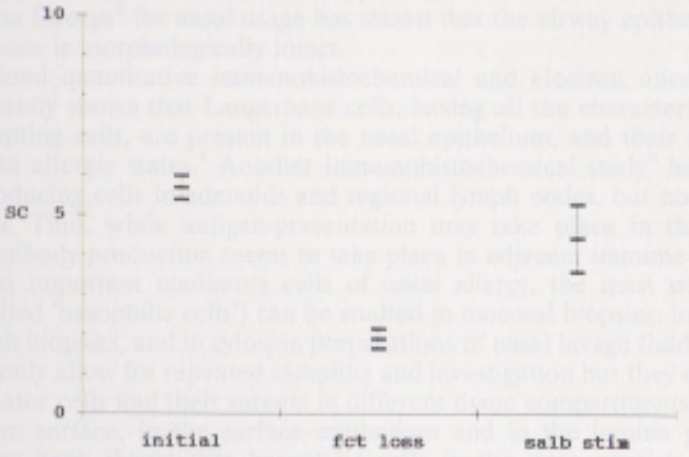

Fig. 2 Average signal signal consistency (SC) with standard deviation of the "initial," "function loss," and "salbutamol stimulation" condition (six subjects).

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Chairman's Introduction

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Allergic airway diseases present a growing problem in industrialized urban areas. Asthma is most serious, but allergic rhinitis is most frequent and, in addition, it can serve as an easily accessible model for the study of pathoanatomy and pathophysiology of the allergic diseases.

The temporal course of the nasal response to an allergen challenge in the laboratory can, according to Naclerio,[1] be described as consisting of an immediate or early response (ER), lasting for less than 1 hour, a late response (LR)(1-12 hours), and a rechallenge response (RCR)(response to a new challenge within 12-24 hours).

The ER is characterized by serial sneezing, profuse watery hypersecretion, and nasal blockage. The LR, at least in our experience,[2] consists of partiel and prolonged nasal blockage, a few incidental sneezes and nose blowings, but these symptoms do not have a well-defined peak in time. Thus, in contrast to the bronchial response to allergen, the nasal response does not exhibit a clear biphasic symptom curve. The RCR to a new allergen challenge within 24 hours will often, but not always, show increased specific and non-specific responsiveness.

The underlying immunological, histological, cytological and biochemical processes can in the nose be studied in such great detail that it makes allergic rhinitis unique among allergic and immunological diseases.

Mucosal biopsies can be taken for quantitative light microscopy, immunohistochemistry and electron microscopy with little more inconvenience than a venipuncture. In contrast to the lower asthmatic airways, where small pairs of forceps easily damage the surface epithelium - which has made pulmonologists believe that even light asthma is associated with epithelial destruction - the excellent large Geritsma forceps[3] for nasal usage has shown that the airway epithelium in the allergic nose is morphologically intact.

A combined quantitative immunohistochemical and electron microscopic study has recently shown that Langerhans cells, having all the characteristics of antigen-presenting cells, are present in the nasal epithelium, and their number is increased in allergic states.[4] Another immunohistochemical study[5] has identified IgE-producing cells in adenoids and regional lymph nodes, but not in the nasal mucosa. Thus, while antigen-presentation may take place in the nasal lining, IgE antibody production seems to take place in adjacent immune tissues.

The most important mediators cells of nasal allergy, the mast cells and basophils (called 'basophilic cells') can be studied in mucosal biopsies, in scrape biopsies, brush biopsies, and in cytospin preparations of nasal lavage fluid. These methods not only allow for repeated sampling and investigation but they can also identify mediator cells and their subsets in different tissue compartments, i.e. on the epithelium surface, in the surface epithelium and in the lamina propria. Results so far have shown that basophilic cells in the nose consists of few basophils and many mast cells, which probably belong to different subsets ('mucosal mast cells', 'connective-tissue mast cells'). The relative proportion of these subgroups of basophilic cells varies between
nasal surface fluid, surface epithelium, and lamina propria. There is an influx of basophilic cells following allergen challenge, and their number is

increased on the epithelial surface and in the surface epithelium. These cells, especially those close to the surface, show signs of degranulation following allergen challenge.[6]

Eosinophils are characteristic of nasal allergy and they are recruited to the nose 4 - 6 hours after an allergen challenge.[7] Some authors have found and increased number already after 30 minutes.[8] The eosinophils release cytotoxic proteins, but their role in nasal pathophysiology remains unclarified. There does not appear to be eosinophil-induced epithelial destruction, but eosinophil products possibly contribute to nasal hyper-reactivity.

Provoked nasal secretions can directly be collected for biophysical and biochemical studies of airway secretions. Nasal lavage fluid can be sampled even from normal noses for the identification and counting of cells as well as the measurement of mediators and markers of allergic reactions. Naclerio[1] has in recent years with success used a lavage technique starting with a series of nasal washings in order to obtain 'basal values'. This type of studies has shown release of histamine both during the ER and during the LR. However, the ER histamine level has not exceeded pre-lavage level and LP histamine release correlates poorely with nasal symptoms. Release of another mast-cell-derived substance, prostaglandin D_2, is shown during the ER and not during the LR, indicating that histamine in the LR is released from basophils and not from mast cells.[1]

Also markers of plasma exudation (albumin, bradykinins) can be sampled from the nasal mucosa using the lavage technique. Allergen challenge induces a rapid-in-onset and transient increase in plasma markers. It has been hypothesized that plasma exudation is a pathogenic factor in allergic inflammatory airway disease.[9]

Neuropeptides can also be studied in the human nose. Their number is large but their significanse for nasal allergy is uncertain.

The analysis of putative mediator substances, neurotransmittors and neuropeptides can be supplemented by intranasal challenge withe the substance in question, and by study of the effect on the allergic reaction from pretreatment with the specific antagonist. So far only histamine has got a firmly established role as an important mediator of nasal allergy. The role played by the high number of other putative mediators seems limited and confined to nasal congestion and perhaps mucus hypersecretion.

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PATHOPHYSIOLOGY OF THE NASAL MUCOSA

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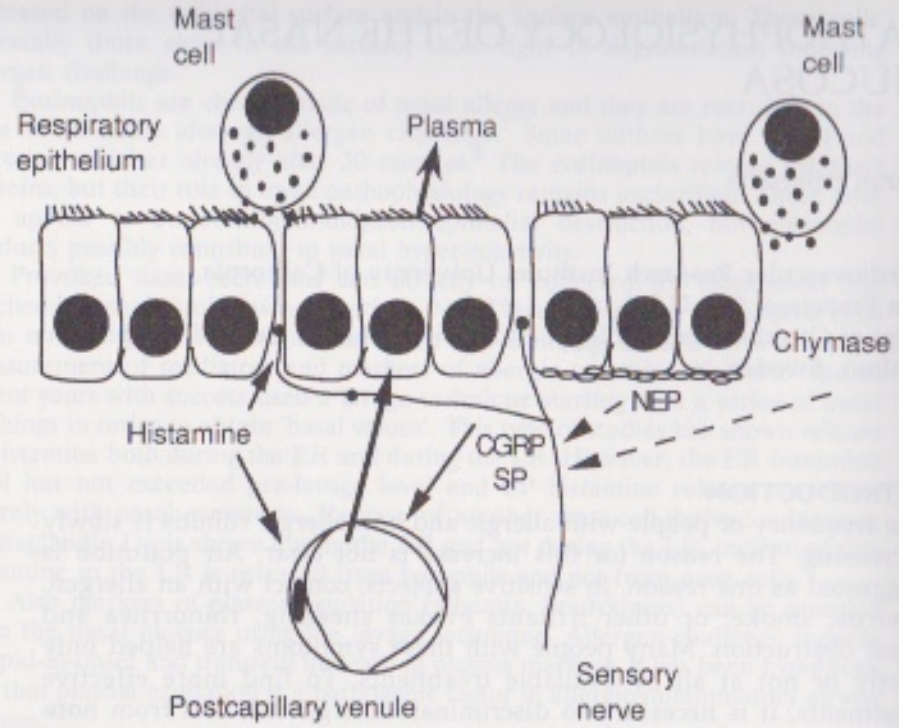
INTRODUCTION

The frequency of people with allergic and non-allergic rhinitis is slowly increasing. The reason for this increase is not clear. Air pollution is suggested as one reason. In sensitive subjects, contact with an allergen, a virus, smoke, or other irritants evokes sneezing, rhinorrhea and nasal obstruction. Many people with these symptoms are helped only partly or not at all by available treatments. To find more effective treatments, it is necessary to discriminate allergic rhinitics from non-allergic rhinitics. Yet, the only clinically useful tool to do this is nasal provocation with the proper allergen.

To date, it is known that the pathophysiology of allergic rhinitis involves a cascade of mediators released from inflammatory cells. For several of these mediators, the effect on nasal symptoms is known. However, the symptoms of allergic rhinitis are regulated by a complex interaction of mediators not only from inflammatory cells but also from immune system, nerves, blood vessels, and epithelial cells. Understanding the interaction of mediators from these sites should help elucidate the pathophysiology of the nasal mucosa.

INTERACTION OF MEDIATORS FROM CELLS AND NERVES

The interaction between inflammatory cells, in particular mast cells, and nerves have been suggested to occur (Payan & Goetzl, 1987). One basis for such an interaction is that some mast cells are located close to sensory nerve endings, implying that mast cell mediators are released into the same tissue microenvironment as neurotransmitters are released. Some of these mediators released from mast cells can activate sensory nerves, thereby evoking reflex symptoms such as sneezing, secretions, and possibly also congestion. On the other hand, activation of sensory nerves can release neurotransmitters, which stimulate inflammatory cells (Fig.).



Schematic figure of the nasal mucosa with possible interactions between mast cells, epithelial cells, sensory nerves and blood vessels. The sensory nerves contain the neuropeptides substance P (SP) and calcitonin gene-related peptide (CGRP). SP can be degraded by neutral endopeptidase (NEP) from the epithelial cells and by chymase from the mast cells.

ACTIVATION OF SENSORY NERVES BY MAST CELL MEDIATORS

The initial interaction between antigen and antibody on the mast cell surface is thought to take place on the surface of the nasal mucosa, resulting in release of mediators, such as histamine, prostaglandins, and leukotrienes (Pipkorn et al., 1988). These inflammatory mediators evoke sneezing, rhinorrhea and nasal obstruction by a direct or an indirect action. Mediators derived from mast cells can act directly on blood vessels, but they also act indirectly on vessels and glands by activating sensory or motor nerves. In evidence that nerves are involved in allergic rhinitis, it is known that local anaesthesia can block the effect of allergen provocation (Konno & Togawa 1979).

The activation of sensory nerves can evoke axon reflexes involving release of neuropeptides, and also evoke classical reflexes that have efferent effects via parasympathetic and sympathetic pathways. The

sensory nerves contain neuropeptides such as calcitonin gene-related peptide (CGRP) and substance P (SP), and the efferent nerves contain neuropeptides such as vasointestinal peptide (VIP), and neuropeptide Y (Uddman & Sundler, 1987). Locally released neuropeptides diffuse and are rapidly degraded. However, some neuropeptides such as CGRP, SP, somatostatin, and VIP, have been isolated from nasal secretions in allergics and non-allergics (Walker et al., 1988).

In contrast to the inflammatory mediators, the neuropeptides do not generally increase immediately after allergen provocation. In allergics, the concentration of SP immediately after provocation with allergen does not differ from that after methacholine (Tønnesen et al., 1988). Furthermore, the concentration of CGRP and SP in nasal secretions immediately after provocation does not differ from that before challenge (Petersson et al., 1990). In contrast, the concentration of CGRP increases at 6 and even at 24 hours after allergen provocation (Walker et al., 1988). The fact that CGRP increases at 6 hours after provocation implies that the increase coincides with the late phase reaction. The late phase reaction is characterized mainly by nasal congestion and, unlike the acute phase, no sneezing and rhinorrhea. Some believe the late phase reactions to be more relevant for chronic diseases but only about 50% of allergic rhinitics have a late phase reaction (Ferguson & Davies, 1991). Thus, CGRP might be a marker for the state of chronic allergic rhinitis, and also suggest the involvement of sensory nerves in allergic rhinitis.

NASAL PROVOCATION WITH NEUROPEPTIDES

To further test whether neuropeptides are involved in the symptoms of allergic rhinitis, two neuropeptides, CGRP and SP, have been administered in an attempt to mimic the symptoms. However, CGRP did not evoke any nasal symptoms (Geppetti et al., 1988). The reason might be that symptoms were recorded in the acute phase. Thus, symptoms in the late phase are not excluded. SP had no effect on secretions (Petersson et al., 1989). Its effect on airway resistance is contradictory. In one study, SP increased the nasal airway resistance in atopics but not in normal individuals (Devillier et al., 1988), whereas in another study SP caused no increase in atopics or in normal individuals (Miadonna et al., 1988). In all provocations using SP, systemic effects appeared, implying that SP was rapidly absorbed and transported by the circulation to distant sites.

ENZYMATIC DEGRADATION OF NEUROPEPTIDES

The reason that the neuropeptides in humans, unlike anesthetized animals, have not yet been convincingly shown to evoke any nasal symptoms might be due to that the neuropeptides are rapidly degraded. There are several pieces of evidence for the rapid degradation of neuropeptides. Secretions from allergic rhinitics and nasal mucosa

from normal individuals can rapidly degrade SP (Petersson et al., 1989, Petersson et al., Unpublished observation). This degradation might be explained by the action of multiple enzymes. Mast cells release not only mediators such as histamine but also enzymes such as tryptase and chymase. Chymase can degrade SP and VIP (Caughey et al., 1988). Thus, mast cells interact with neuropeptides not only by release of mediators that activate nerve endings but also by release of enzymes that degrade the peptides released. In the respiratory epithelium, there are also another enzymes, neutral endopeptidase (NEP)(Petersson, Ueki, Nadel, Unpublished observation). Thus, NEP is located close to the sensory nerve endings from which the neuropeptides are released. SP but not CGRP is degraded to a large extent by NEP (Katayama et al., 1991). This might explain that an increase of the concentration of CGRP, but not of SP, was detected in nasal secretions at 6 and 24 hours after allergen provocation (Walker et al., 1988).

ACTIVATION OF INFLAMMATORY CELLS AND BLOOD VESSELS BY NEUROPEPTIDES

The other direction of the proposed interaction of inflammatory cells and neuropeptides, the activation of inflammatory cells by neuropeptides, is illustrated by the observation that VIP and SP are present not only in nerves but also in human eosinophils (Aliakbari et al., 1987). Furthermore, SP stimulates lymphocytes from allergics more than those from non-allergics (Nilsson et al., 1989), and SP primes human neutrophil activation (Perianin et al., 1989). However, in humans, unlike animals, SP does not release histamine from mast cells.

Neuropeptides also interact with blood vessels in a two-way fashion: in one direction neuropeptides like inflammatory mediators increase vascular permeability, permitting leakage of plasma including albumin and immunoglobulins. In the other direction, the leakage of plasma forces allergen and other noxious material out of the mucosa, and help neutralize the effects of allergens (Persson et al., 1991). Thus, in allergic rhinitis, plasma is present in the same microenvironment as mast cells and sensory nerves.

In summary, the course of allergic rhinitis is regulated by a complex interaction between inflammatory cells, nerves, immune system, and blood vessels.

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The Impact of Immunotherapy on the Pathophysiology of Ragweed Pollen Allergy

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INTRODUCTION

Immunotherapy (desensitization) for allergic rhinitis is an efficacious treatment extensively used in modern medicine. Investigation into the mechanism for its efficacy has shown a variety of immunological changes including: a) an initial rise in serum IgG_1 antibodies followed by a change to an IgG_4 response (1,22); b) suppression in the usual seasonal rise in IgE antibodies that follows environmental exposure; c) increase in specific IgA and IgG antibodies in nasal secretions; d) reduced *in vitro* lymphocyte responsiveness to allergens; e) generation of specific suppressor T cells; f) blunting of the late skin and bronchial responses to allergen provocation; g) the development of antigen-specific mononuclear cells and h) a reduction of a mononuclear cell-derived histamine-releasing factor (2,8,13,19,21). Despite these findings, the precise efficacy of immunotherapy and its underlying mechanism of action remain unclear (9).

As a means to augment our understanding of immunotherapy, we investigated its effect on the response to nasal challenge. We have developed a laboratory nasal antigen challenge which analyzes secretions recovered by lavage. Using this model, we showed: a) that the immediate allergic reaction is associated with an elevation of symptoms scores and mediator release (histamine, TAME-esterase activity, kinins, sulfidopeptide leukotrienes, prostaglandin D_2) (4-6,10,14,20); b) a late phase with recrudescence of symptoms and a second peak in mediator levels 3-11 hours after antigen challenge (15); c) specific hyperreactivity to antigen hours after a preceding antigen challenge (25); d) nonspecific hyperreactivity to histamine after antigen challenge (26) and e) cellular infiltration (3,15). In view of the striking success of this nasal challenge technique to quantify a panoply of biochemical mediators and cells during an allergic reaction, we undertook a variety of studies to investigate the impact of allergen immunotherapy on such parameters.

METHODS AND RESULTS

We performed a series of studies with some inherent similarities. Immunotherapy was given as weekly injections until a maintenance dose was reached, usually within a 3-month period. Injections were then switched to biweekly. We report the maintenance dose given. Nasal challenges were performed as previously described. The subjects were challenged with the antigen extracts used for immunotherapy, and nasal lavages were used to monitor the response.

We first performed a double blind study involving 21 subjects treated with a maintenance dose of 2 µg of *Amb a I* over a period of 8 months and 20 matched subjects who received placebo injections. Symptoms and medication diaries recorded during seasonal exposure demonstrated the clinical efficacy of the administered immunotherapy dose. The immunologic responses of the actively treated subjects in this

study consisted of a marked increase in serum IgG antibody titer to ragweed. The level of specific IgE antiragweed antibody rose after the season in the placebo group but not in the actively treated group.

Both study groups underwent identical nasal challenges with ragweed antigen extract both before and during immunotherapy. Between-group analysis showed that immunotherapy significantly reduced the levels of histamine, TAME-esterase activity and kinins, as well as the symptoms of rhinorrhea and congestion generated during the early response to nasal challenge (Fig. 1). Assessment of treated subjects by successive yearly follow-up challenge demonstrated a progressive reduction in histamine release and the clinical response to nasal challenge.

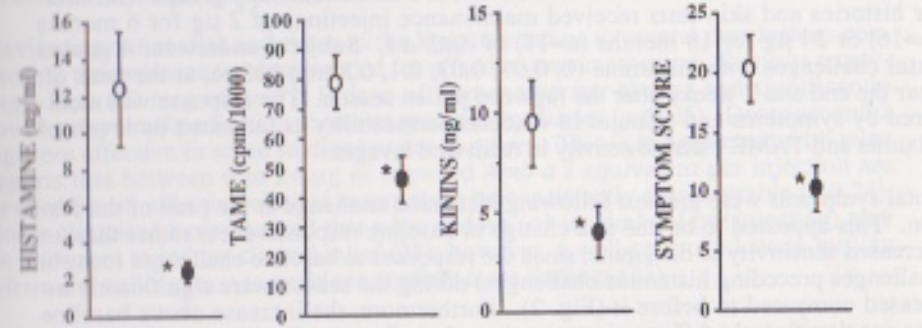

Fig. 1: Immunotherapy decreases the net change from baseline of mediators and symptoms during the early allergic response. The subjects on placebo are depicted by the open circles (n=20) and those on immunotherapy by the closed circles (n=21). *p<0.02 vs placebo. (Mean ± SEM)

Within-group paired analysis also showed a partial reduction of late and rechallenge (priming) mediators and symptoms in those subjects who underwent immunotherapy. Interestingly, there was no decrease of the late response of an individual without an antecedent decrease of the early reaction. We also studied the impact of immunotherapy on skin testing as measured by intradermal endpoint titrations performed on each of the study groups. A significant reduction in both the early and, particularly, the late cutaneous reaction occurred in the treated group.

In other studies, we have shown that the inhibition of the acute response to ragweed occurs within 3 months of starting therapy and that there is no difference between the response of children and adults in terms of skin test reactivity (11,12).

We undertook a study of other effects of immunotherapy on eosinophil influx into nasal mucosa. Thirteen subjects who received no treatment, 10 who received 2 µg *Amb a I* and 6 who received 24 µg *Amb a I* were evaluated. The percentage of eosinophils in nasal lavages was determined both prior to and 24 hours after nasal challenge with ragweed extract. No differences between groups were seen before antigen challenge. The nonimmunotherapy group demonstrated a significant increase in the percent of eosinophils, from 26 to 69.5% ($p<0.008$), in response to antigen provocation, whereas the treated groups showed no significant changes. This is the first demonstration that immunotherapy reduces eosinophil migration into the nose.

This effect on eosinophil influx was then confirmed by a seasonal study of 45 subjects who were divided into groups based on a maintenance dose of *Amb a I* and

duration of treatment: group 1 (n=10), no treatment; group 2 (n=12), 1 year at 2 µg; group 3 (n=10), 2 years at 2 µg; and group 4 (n=9), 3 years at 24 µg. Nasal mucosal brushings were done during the ragweed season. The highest dose of immunotherapy led to a significant reduction in the percentage of eosinophils in the nasal brushings (18 vs 8.4; $p<0.004$), and this was associated with a significant reduction in symptoms reported during the season. Combined, these studies clearly show that immunotherapy reduces the eosinophilic influx following antigen exposure.

We also investigated antigen-induced hyperresponsiveness by studying the effect of immunotherapy on nasal challenge with histamine before, at the peak of and after the ragweed season. Nineteen subjects with ragweed hay fever confirmed by a positive intradermal skin test served as controls, whereas 2 immunotherapy groups with similar histories and skin tests received maintenance injections of 2 µg for 6 months (n=16) or 24 µg for 18 months (n=11) of *Amb a I*. Subjects underwent 4 graded nasal challenges with histamine (0, 0.01, 0.03, 0.1, 0.3 mg) before, at the peak of, near the end and 2 weeks after the ragweed pollen season. The response was monitored by symptoms and changes in vascular permeability as indicated by levels of albumin and TAME-esterase activity in recovered lavages.

Total symptoms were greatest following histamine challenge at the peak of the season. This appeared to be due to a change in baseline responsiveness rather than an increased sensitivity to histamine, since the responses to baseline challenges (control challenges preceding histamine challenges) during the season were significantly increased compared to before it (Fig. 2). Furthermore, the increase above baseline was not significantly different between these 2 challenges. Similar results for levels of albumin and TAME-esterase activity were found. High dose immunotherapy prevented the increase in baseline measurements and, thus, changes in responsiveness to histamine (Fig. 2).

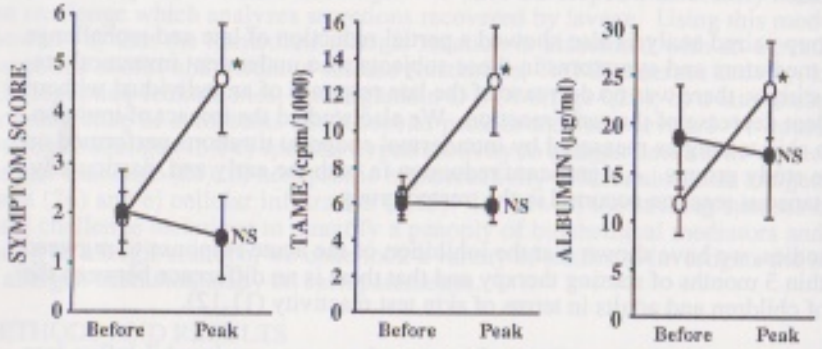

Fig. 2: Symptoms and mediators after the baseline (control) challenge before and at the peak of the ragweed season for the control group (open circles, n=19) and the group on high dose immunotherapy (closed circles, n=11). Baseline responses increased significantly (*$p<0.02$) at the peak of the season as compared to before it in the control group. This was inhibited by high dose immunotherapy. NS=nonsignificant. (Mean ± SEM)

DISCUSSION

Using nasal antigen challenge, we have made significant progress towards understanding the underlying pathophysiological and immunobiochemical events occurring between antigen exposure and the manifestation of the clinical symptoms of allergic

rhinitis. It is within this conceptual framework that we have been able to gather considerable data concerning the efficacy and mechanism of action of immunotherapy in the alleviation of symptoms of allergic rhinitis.

Specifically, immunotherapy appears to be associated with: a) a reduction in symptom/medication scores recorded during seasonal exposure; b) progressive annual reduction in symptoms and histamine release upon nasal challenges with respect to the acute and allergic response; c) a decrease in the late phase response, which, in contrast to previous reports, did not occur without a reduction in the early response (18, 27); d) marked increase in specific serum IgG antibody titer; e) reduced hyperreactivity to histamine challenge and f) reduced eosinophil migration into the nasal mucosa as assessed by antigen challenge and seasonal sampling.

Reviewing our studies and those in the literature led us to several conclusions concerning the maintenance dose needed for effective immunotherapy. Subjects receiving a high (20 mcg of *Amb a I*) dose of immunotherapy always had significantly lower symptoms/medication scores as recorded by diaries ($p<0.05$). Doses around 2 µg were effective in some studies but not in others. This is in agreement with most reports that between 6 to 24 µg of ragweed *Amb a I* equivalent per injection are needed for an effective clinical response to be consistently demonstrable (7,9,24). Some clinicians have reported that a lower dose (<1 µg *Amb a I* per injection) may be sufficient to induce clinical relief (28); however, a well-controlled study by Van Metre and colleagues was unable to confirm these findings (23).

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In Human Nasal Mucosa, Interleukin-5 Accumulates and Degranulates Eosinophils, as well as Increases Responsiveness to Histamine.

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INTRODUCTION

In recent years, interleukin 5 (IL-5) and secretory IgA were recognized as eosinophil activation and/or degranulation factors. IL-5 affects precursor cells in bone marrow and promotes the differenciation and proliferation of eosinophils. Also, IL-5 has been reported to prolong the survival rate of mature eosinophils, and, enhance LTC_4 production as well as cytotoxicity. Although there is a difference in opinion, the majority of investigators reported that IL-5 is a eosinophil chemoattractant. Of interest, IL-5 has been shown to affect IgA synthesis. As such, IL-5 has diversified effects, however, there are few or no reports which have confirmed these effects in vivo, particularly in humans. When taking into consideration the differences in species as well as the differences in their organs, it is necessary to evaluate the effect of IL-5 in human nasal mucosa in vivo. As well, it must be determined whether or not IL-5 is actually present in nasal mucosa and nasal lavage fluid.

In the present study, at first, we examined the expression of IL-5 mRNA in nasal mucosa and measured the amount of IL-5 in nasal lavage fluid obtained after an antigen challenge. Then, we assessed the effect of recombinant human IL-5 (rhIL-5) on eosinophils accumulation and degranulation in human nasal mucosa, in vivo. At the same time, we investigated the change of histamine reactivity in nasal mucosa attributable to the degranulation of eosinophils. The effect of secretory IgA on ECP release from eosinophils was also studied.

RESULTS

1. The expression of IL-5 mRNA in nasal mucosa and the changes in the amount of IL-5 in nasal lavage fluids after an antigen challenge.
(1) Expression of IL-5 mRNA in nasal mucosa after an antigen challenge.

To determine whether or not mRNA for IL-5 is expressed in nasal mucosa after specific antigen challenge, amplified cDNA derived

from mRNA in nasal mucosa were analized.
The results are shown in Fig. 1. Lane 1 represents the results of the electrophoresis of the PCR product from the nasal mucosa of the subjects with sinusitis. Lane 2 represents the results of the nasal mucosa in the subjects with nasal allergy without antigen challenge. And,lane 3 shows the results 4 hours after the challenge. After the challenge, the specific band could be confirmed at the same 390bp position as that for the PCR product of the cDNA probe, used as the positive control shown in lane 4. Moreover, when the PCR products of the cDNA probe and the challenged nasal mucosa is digested by Taq. I, bands in target sizes of about 270bp and 120bp were successfully obtained. These results are shown in lanes 5 and 6 respectively.

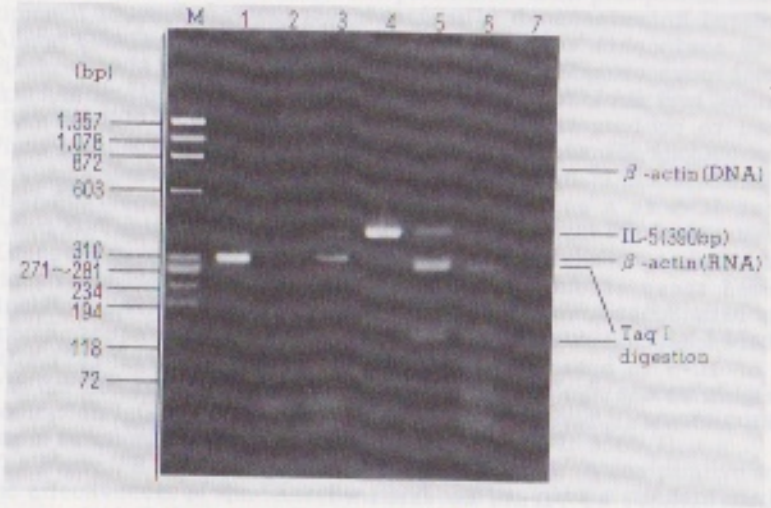

Fig. 1. PCR-assisted IL-5 mRNA amplification of nasal mucosa.

(2) Changes in the amount of IL-5 in nasal lavage fluids.
Twelve adult subjects (1 woman, 11 men) between 21 and 50 yrs of age with Japanese cedar pollinosis were studied.
There were 5 cases with a significant increase of IL-5 after the challenge. In 3 out of the 5 cases, the increases were observed only in the late phase. Another two showed biphasic increases. For 8 cases in which an increase in IL-5 was not observed, another measurement of IL-5 in the nasal lavage fluids was performed 24 hours later, but significant increases were not observed. (Data not shown).

2. The effect of rhIL-5 and secretory IgA on nasal mucosa
(1) Changes in eosinophil count, the amount of ECP and epithelial cell count in nasal lavage fluids after nasal applications of rhIL-5.

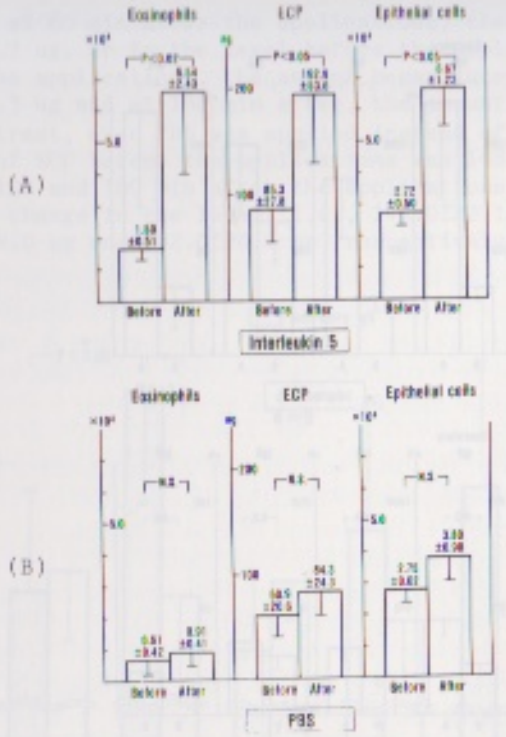

Fig. 2. Number of eosinophils, amount of ECP and number of epithelial cells in the nasal lavage fluids before and after the applications of rhIL-5 (A) and PBS (B). Results are expressed as mean ± SE.

(2) Changes in the amount of immunoglobulin in nasal lavage fluid after nasal applications of rhIL-5

Secretory IgA in the nasal lavage fluid increased significantly from 322.6±60.7 ug to 1,245.0±462.7 ug after applications ($p<0.05$) (Fig. 7). Likewise, IgA increased from 270.8±58.8 ug to 838.9±278.0 ug ($p<0.05$), IgG and IgM from 128.2±40.9 ug to 203.9±66.6 ug ($p<0.1$) and 33.7±19.6 ug to 116.2±90 ug ($p<0.05$), respectively. In contrast, with the applications of PBS, secretory IgA, IgA, IgG, and IgM showed no significant changes.

(3) Changes in histamine nasal reactivity after applications of rhIL-5 and ECP

The frequency of sneezing and NAR induced within 60 min by 20 ul of 0.25% histamine (x 2) were not significantly affected by the applications of rhIL-5 of 0.1% BSA-added PBS. In contrast, the weight of nasal discharge showed a tendency toward increase from

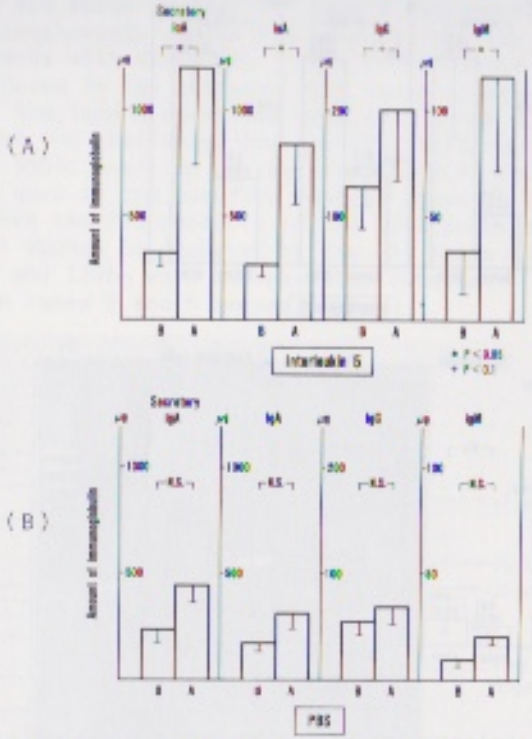

Fig. 3. Amount of secretory IgA, IgA, IgG and IgM in the nasal lavage fluids before and after the applications of rhIL-5 (A) and PBS (B). Results are expressed as mean ± SE.

1.86±0.30 g before the applications of rhIL-5 to 2.39±0.39 g after the applications ($p<0.1$), whereas no significant change was observed after the applications of 0.1% BSA-added PBS, that is, from 1.83±0.36 g to 1.73±0.46 g.
Prior to applications of ECP, the weight of the nasal discharge induced by histamine within 60 min was 1.62±0.28 g, and this showed a tendency towards an increase to 1.91±0.27 g after the applications of ECP ($p<0.1$).

(4) Changes in the amount of ECP in nasal lavage fluids after applications of secretory IgA

The amount of ECP in the nasal lavage fluid before the applications of secretory IgA (and after the applications of rhIL-5) was 142.0± 26.6 ug, however, it increased significantly to 196.1±31.3 ug at 30 min after the applications of secretory IgA (Fig. 4).

Thereafter, at 60 min after the applications, the level decreased to 123.3±25.7 ug, or to the level before the applications. At 120 min after the applications, the amount began increasing gradually to 159.6±32.3 ug and at 180 min after, the amount was 179.7±41.7 ug. In contrast, when PBS was applied instead of secretory IgA, the amount of ECP before the applications was 148.9±19.4 ug, but at 30, 60, 120 and 180 min after the applications, there was no significant change in the level, i.e., 143.0±22.1 ug, 148.8±21.0 ug, 137.1±24.0 ug and 142.0±20.1 ug, respectively.

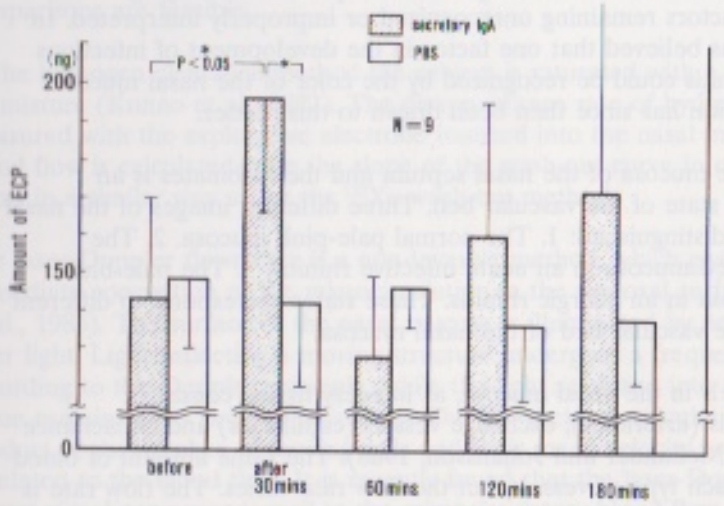

Fig. 4. Changes in amount of ECP in nasal lavage fluids after the applications of secretory IgA or PBS.

DISCUSSION

IL-5 is known to have selective and wide range of effect on mature eosinophils such as involvement in their defferenciation and proliferation.
In the present study, we focused on the effect of IL-5 on eosinophils in nasal mucosa.
Considering the fact that IL-5 induce production of IgA and that eosinophils have IgA receptors, the results in this study suggests the involvement of a series of reaction consisting of (1) IL-5 causing IgA production in the immune mediating cells, (2) binding of IgA with the secretory component released from cells of the serous gland or epithelial cells within the nasal mucosa, (3) degranulation of eosinophils mediated by secretory IgA and IgA, (4) release of granular proteins such as ECP, (5) epithelial damages, and (6) development of sensitivity for histamine of the nasal mucosa.

BLOOD FLOW IN THE ALLERGIC NASAL MUCOSA

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The etiology of nasal disease is complex with important underlying constitutional factors remaining unrecognized or improperly interpreted. In early days, it was believed that one factor in the development of infectious and allergic rhinitis could be recognized by the color of the nasal mucosa. Very less attention has since then been drawn to this matter.

The color of the mucosa of the nasal septum and the turbinates is an indicator of the state of the vascular bed. Three different images of the nasal mucosa can be distinguished: 1. The normal pale-pink mucosa. 2. The reddish congested mucosa in an acute infective rhinitis. 3. The pale-bluish congested mucosa in an allergic rhinitis. These states correspond to different conditions in the vascular bed of the nasal mucosa.

The blood vessels in the nasal mucosa, as in every tissue, consist of resistance vessels (arterioles), exchange vessels (capillaries) and capacitance vessels (veins) (Mellander and Johansson, 1968). The same amount of blood flows through each type of vessels, but the flow rate varies. The flow rate is highest in the arteries because they are fewer in comparison with other types of vessels. The flow rate in the capillaries is very slow, and only some capillaries are open during normal conditions. In an acute infective rhinitis, there are more open capillaries, which cause a more reddish mucosa (Bende, 1983). The capacitance vessels include ordinary veins and sinusoids. The sinusoid system is characteristic for the nasal mucosa and it occupies most of the volume, especially in the turbinates and the middle of the septum. Changes in blood volume in the sinusoids cause considerable changes in the mucosal thickness.

Several methods are available for studying the nasal vascular bed in man. These methods provide information about different blood vessels. The function of the capacitance vessels, regulating the blood content of the nasal mucosa, is often measured indirectly by rhinomanometry. The blood flow, however, is regulated independently of the blood content (Åkerlund and Bende, 1989). Methods to study the blood flow in man will be briefly recapitulated.

The ^{133}Xe wash-out method measures the mean blood flow or mean perfusion of the mucosa during a certain period (Bende et al., 1983). This method is based on the injection of a small amount of radioactive xenon into the mucosa. The disappearance of the isotope is recorded with a scintillation detector placed over the nose. The disappearance rate is directly related to the blood flow. The xenon is freely diffusible in the mucosa. When the isotope diffuses into capillaries, it is taken away by the blood stream and washed out by the venous blood. The isotope disappears by the ventilation and no recirculation occurs. The ^{133}Xe wash-out method has been standardized for many other tissues in man and experimental animals. The blood flow is expressed in ml/min/100 g tissue and inter-individual comparisons are feasible.

In the hydrogen clearance method the subject is saturated with a hydrogen-air mixture (Konno et al., 1982). The disappearance rate of hydrogen is measured with the explorative electrode inserted into the nasal mucosa. The blood flow is calculated from the slope of the wash-out curve in quantitative terms in a similar way as for the ^{133}Xe wash-out method.

The laser-Doppler flowmeter is a non-invasive method, which gives an immediate conception of the microcirculation in the mucosal surface (Olsson et al., 1985). The surface of the nasal mucosa is illuminated by neon-helium laser light. Light reflecting a moving structure undergoes a frequency shift, according to the Doppler principle, while the light scattered into the static tissue remains at its original frequency. The flowmeter is calculating the product of the number of moving cells and their mean velocity, which in turn is related to the blood flow. It is recently found that the laser-Doppler output signal corresponds well to the microcirculatory blood flow in the nasal mucosa as seen in intravital microscopy, although, in this complex vascularity, the absolute blood flow could not be calculated by this instrument (Åkerlund et al., 1991).

The allergic rhinitis has been studied after provocation with antigens applied topically on the nasal mucosa. Immediately after application of the antigen, the subject feels a nasal irritation and urge to sneeze. After a couple of minutes, the nose feels runny and stuffed up. These symptoms could be found before any objective signs are detectable. With higher doses of antigens, more pronounced symptoms are obtained, like sneezes, watery secretion, nasal blockage and symptoms from the eyes and lower airways.

The effect of the allergic reaction on the mucosal blood flow has been studied during the last ten years. The main effect is a pronounced reduced blood flow in the nasal mucosa (Bende et al., 1984). However, there are also studies with other results. Tanimoto and coworkers (1983) provoked with antigen-containing paper discs and studied the blood flow with the hydrogen clearance method. They found a decreased blood flow in the mucosa close to the allergen disc, whereas the blood flow increased at the area 10 mm away from the disc. By the laser-Doppler flowmeter an increased as well as a

decreased blood flow has been found in experimental allergic reactions (Juliusson and Bende, 1987; 1988; 1991: Rangi et al., 1990). Most investigations of the blood flow in the allergic mucosa have been performed by the ^{133}Xe wash-out technique and the results are distinct, a dose-dependent decreased blood flow has been found after allergen provocation (Bende et al., 1984; Holmberg et al., 1988).

Is there a plausible explanation for these results in relation to the symptoms of an allergic rhinitis and the color of the mucosa as it looks like at anterior rhinoscopy?

Early in the allergic reaction, there is probably a local inflammatory response in the nasal mucosa, with a slight increased microvascular blood flow (Juliusson and Bende, 1987; 1988). This effect does not influence the perfusion of the nasal mucosa. After administering more antigen, which induce pronounced symptoms, the nasal mucosal blood flow decreases in a dose-dependent way and a maximal 40 % reduction is observed (Bende et al., 1984; Holmberg et al., 1988). With a pronounced decrease of the blood flow, the pH in the tissue decreases and local mechanisms in the microcirculation try to compensate with vasodilation (Bende et al., 1991). Therefore, we can register both an increase and a decrease in the microcirculatory blood flow during the same time the perfusion of the nasal mucosa is reduced.

Holmberg found that unilateral provocation also induced a dose-dependent decrease in the blood flow of the contralateral side. This effect, but not the symptoms, was abolished when topical anaesthesia was administered to the nasal cavity 20 minutes before the allergen. This strongly suggests that there is a reflex mechanism between the two nasal cavities which could influence the regulation of nasal mucosal blood flow during the allergic reaction (Holmberg et al., 1989; 1989).

The blood flow decreasing effect could be inhibited by histamine-1 antagonists, but not by histamine-2 antagonists (Holmberg et al., 1989; Juliusson and Bende, 1991). This indicates that histamine-1 receptors are involved in the mechanism of the decreased blood flow (Fig. 1). The pale-bluish color of the mucosa, and the findings that a puncture of the allergic bluish mucosa induces more bleeding than usual (Bende et al., 1984), suggests that there is a venous stasis, with filled sinusoids but with a low perfusion through the capillaries.

The clinical importance of a decreased blood flow during an allergic rhinitis is not known. Further studies are needed to explain the pathophysiology of the vascular system in an allergic disease. Still there are questions remain to be answered and one of the most important is: Is there a benefit to the host of a decreased mucosal blood flow in an allergic rhinitis?

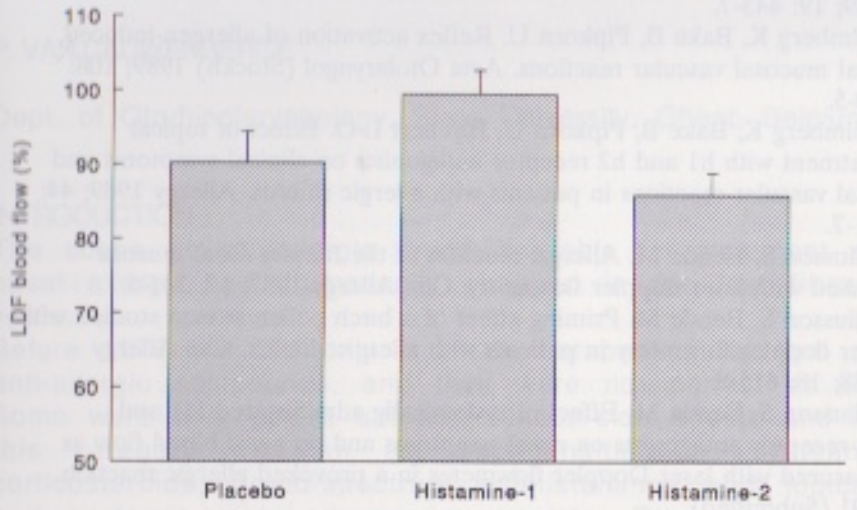

Fig. 1. The effect of pretreatment with placebo, a selective histamine-1 antagonist (terfenadine), and a selective histamine-2 antagonist (cimetidine) on the microcirculatory blood flow in the nasal mucosa after allergen challenge in 12 subjects with birch pollen allergy (Juliusson and Bende, 1991).

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RECENT DEVELOPMENT of ANTI-ALLERGIC DRUGS

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INTRODUCTION

The scope of anti-allergic drugs available for treatment of nasal allergy has dramatically changed in the last fifteen years.
Before 1976 we had only a small therapeutical arsenal of anti-allergic compounds, and they were not perfect at all. Some were very potent but not without side effects and in this category we can list hyposensitisation, systemic corticosteroids, broad-spectrum antihistamines and topical and systemic alpha-adrenergic agonists. Others such as disodium cromoglycate only had a preventive mode of action.
Since then new anti-allergic drugs were developed and are widely used for the treatment of nasal allergy. Their strongest points are a better activity and/or fewer side effects. This led to more rational treatment regimens, especially for the adult active person with symptoms of allergic rhinitis.
We will discuss some properties, specific indications and contra-indications, and the strong and weak points of the most recently developed anti-allergic and symptomatic drugs that are used in the treatment of allergic rhinitis.

SHORT SURVEY OF THE THERAPEUTICAL POSSIBILITIES

When we look at the long chain of reactions that takes place during an IgE-mediated reaction, we realize that - on a theroretical base - there are several sites where we can interfere, in order to inhibit or block this reaction. In practice, these possibilities are still limited but usually sufficient in clinical practice.
Sites where interference is possible include the allergens, the circulating IgE (in a lesser extent), the degranulation of the mastcell, the binding receptors for mediators and the target cells where the mediators of allergy exert their activity.
With regard to the treatment following general principles should be stressed: 1. wherever possible, preventive measures should be taken to minimize medication; 2. a therapy with a

minimal or no side effects should be chosen; 3. individual responses to therapeutic agents must be taken into account though they cannot always be forseen.

ENVIRONMENTAL CONTROL

Preventive measures for hay-fever patients include keeping doors and windows closed on days with peak pollen counts, and avoiding pollen-rich environments. In the case of house dust mite allergy, preventive environmental measures (particularly in the bedroom) should be taken. Recently, spraying of natamycine - an antimycotic drug - on the matrasses was advocated in order to reduce the number of Aspergillus, a mold which is one of the most important food ingredients of Dermatophagoides. The clinical results with this kind of preventive measurement are, however, not satisfactory. In addition, several chemicals with a direct anti-mite activity are used now, but there is no proof yet of clinical activity in mite allergic patients.

IMMUNOTHERAPY

Immunotherapy is another kind of preventive method, and a whole series of activity are described. Immunotherapy (hyposensitisation) induces a competitive inhibition, because blocking IgG antibodies are formed; it results also in a desentisation of mast cells and basophils and it causes a decrease of the specific IgE, after an initial raise. It modifies, in vitro the lymphocyte function. Immunotherapy is now performed with more purified modified allergens which makes their activity stronger. It is usually not given as a first treatment, but rather if the "conservative" treatment fails. In pronounced cases of pollen allergy and house dust mite allergy, hyposensitisation will have positive results in most cases. It should be stressed that the total dose of modified allergen administered must be sufficiently high, that the hyposensitisation must be maintained for a sufficiently long period, and that the administering physician should take every ptrvrntive measure available (7). Topical nasal hyposensitisation is only rarely used, while the results of the trials with sublingual administration of the modified allergen are not known yet.

CROMONES

There is not much news about cromones, the well known mast cell stabilizers with their preventive activity (3,6). Although some new compounds like nedocromyl are developed and commercialized, it does not seem that they have a better activity than disodium cromoglycate itself.

ANTIHISTAMINES

Antihistamines cause a competitive inhibition at the histamine receptors of the target tissues. The antihistamines that are used nowadays are more selective and have a nearly unique acitivity on H1 receptors and most of them do not penetrate the blood-brain barrier. This leads to less side effects so that sedation, dry mouth and other anticholinergic side effects are only rarely occurring, contrary to what is seen with the older broad-spectrum antihistamines. So, the commercialisation of astemizole, terfenadine, cetririzine, loratadine was much wellcomed by the allergic patient. It should be stressed, however, that antihistamines have much less effect on nasal obstruction, which is caused by a variety of pathophysiologic processes, than on the other symptoms, which are more exclusively induced by histamine. It is shown, that antihistamines have also other anti-allergic activities, such as inhibition of histamine release, inhibition of eosinophil chemotaxis, inhibition of PGD2 and LTC4 production and inhibtion of neuropeptide activity. Not all antihistaimes have the same extra properties (1,4,5,8,10).

ANTI-PROSTAGLANDINS AND ANTI-LEUKOTRIENES

The non steroid anti-inflammatory drugs - with an anti-prostaglandin activity - do not have an effect on the symptoms of nasal allergy.

Leukotriene antagonists or inhibitors are not available yet for clinical use, but some have shown to have a very potent activity in inhibiting LTD4 and metacholine induced asthma in man (2).

CORTICOSTEROIDS

Inflammatory cells, such as eosinophils, basophils, neutrophils, etc.. are the most important elements in the late phase of the allergic reaction. Attracted to the site of allergic reaction by chemotactic factors they release their mediators and cause an important inflammatory reaction with edema formation. Corticosteroids, with their potent anti-inflammatory activity, have in this stage the best results in

inhibiting the symptoms, which mainly consist of nasal congestion.
Topical nasal steroids, such as beclomethasone dipropionate, flunisolide, budesonide and Tixocortol-21-pivalate, have a potent activity in controlling most symptoms of allergic and non-allergic rhinitis, including nasal obstruction, without having the side effects of systemic steroids. Recently improvements are made with regard to the delivery system and the galenic form (2,4,9).

SYMPTOMATIC TREATMENTS

Vasoconstricting agents

Symptomatic treatment of nasal congestion include the alpha-adrenergic agonists, like oxy- and xylomethazoline, the noradrenaline releasers, like ephedrine and amphetamine, and the drugs that prevent re-uptake of noradrenaline, such as cocaine and tricyclic antidepressants. Long time use of these drugs, however, causes irreversible damage to the blood vessels of the mucosa, while they usually also have a rebound effect and an influence on the cilia.

Ipratropium bromide

Topically applied ipratropium bromide has a potent anti-cholinergic activity and is indicated in patients with watery rhinorrhea; it does not have the side effects of systemic anticholinergic drugs. However, it does not have an activity on nasal congestion, because in the postganglionic para-sympathetic nerves acetylcholine is the mediator responsible for stimulation of the seromucous glands, while VIP causes vasodilation (4).

Other possibilities

In cases of nasal congestion resistant to medical treatment, cryotherapy of the inferior turbinates may be helpful, because it causes a fibrosis in the lamina propria and a (temporary) destruction of the postganglionic parasympathetic nerve fibres.

CONCLUSION

The availability of the new anti-allergic drugs makes it possible to provide the allergic rhinitis patient with a more appropiate and individual treatment with few side effects.

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Drug treatment for allergic rhinitis: a clinical immunologist's view

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The cells central to the allergic reaction, the mast cell and basophil have important physiological functions, including killing of parasites and tumour cells, and participation in wound healing. The IgE arm of the allergic response also has important functions. The high affinity IgE Fc receptor that arms mast cells and basophils is well known. However there is at least one additional, low affinity IgE Fc receptor (Gordon et al (1989): also known as CD23. CD23 not bound to IgE is cleaved into smaller, non cell bound fragments known as soluble CD23 which stimulate B cells and IgE production. When bound to IgE its functions include killing of parasites by macrophages, monocytes, eosinophils and platelets, enhancement of phagocytosis of IgE coated particles, and stimulation of release of inflammatory mediators from monocytes, eosinophils and platelets (Delespesse 1989). CD23 may also have a role in antigen presentation in both the initiation of an immune response, and for the continuing stimulation of already established humoral responses: of considerable interest in this respect was the report at this meeting by Dr. Fokkens of CD23 positive Langerhans cells in the nasal mucosa.

The physiological functions for the various components of the allergic response are important and therefore we would expect them to be difficult to abrogate or even modify in a major way. So far attempts to do so have not been particularly successful, but even if in the future we find the pharmacological means to block such reactions completely, we should anticipate unexpected and possibly quite unacceptable side effects from this.

The mechanism of the allergic response has been well reviewed already. Every step in the complex process offers the potential for a therapeutic intervention. To date the possibility that the initial sensitisation process can be blocked has not really been explored. While children at high risk of developing allergic disease can be identified on the basis of family history and cord blood IgE levels, attempts to modify the evolution of allergic diseases in such patients are still in their infancy (reviewed by Zeiger 1986).

Triggering of mast cells and basophils leads to release of a large series

of mediators (Table 1). Increased vascular permeability allows the accumulation of oedema fluid which contains other inflammatory molecules such as complement components, immune complexes, kinins, and coagulation factors. Changes in the endothelial cells allow attachment and egress of inflammatory cells, contributing to the ongoing inflammation. The role of neuropeptides in allergic rhinitis is far from clear, but may well be important also.

Table 1: Mediators in allergic rhinitis

Itch	Histamine	(? PG by H^1 Effect)
Sneeze	Histamine	LTC_4, D_4, E_4
Rhinorrhoea	Histamine	LTC_4, D_4, E_4 ACh PAF
Obstruction	Histamine	LTC_4, D_4, E_4 ACh PAF KININS
	(+late phase r^n : LTB_4, NCF, ECF - A etc)	

LT = Leukotriene PAF = Platelet Activating Factor

PG = Prostaglandin ACh = Acetyl Choline

In understanding this phenomenon it is important to learn from the observations made in the lower respiratory tract. Bronchial asthma is characterised by a state of chronic inflammation and non specific hyperresponsiveness. In allergic rhinitis repeated allergen challenges lead to a heightened response (Naclerio 1991), presumably due to the presence of an inflammatory infiltrate, including basophilic cells both in the tissues and on the mucosal surface. The concept of nasal hyperresponsiveness, accepted in non allergic rhinitis, may occur in allergic rhinitis as well (Mullins et al 1989).

How then do these observations translate into rational clinical practice? Allergen avoidance is clearly the treatment of choice, but may not be practical. Exposure to airborne allergens such as pollens, and fungal spores cannot be avoided without drastic lifestyle changes. Studies on house dust mite avoidance measures show that only the most draconian measures are likely to be of benefit (De Boer 1990). House dust mite sprays have been shown to be active in the laboratory, but so far a translation into improvement in symptoms has not been demonstrated.

In most cases the drug treatment of first choice is an H1 histamine antagonist. Antihistamines are safe, effective, relatively cheap, and have the advantage of being effective against symptoms at multiple

sites. One of the cardinal rules for antihistamine use is "Don't be greedy". Histamine is only one of many mediators released during the allergic reaction, and clinical studies consistently show that a 40-60% reduction in symptoms is all that can be expected from an H_1 antagonist. It is possible to be more specific about the effectiveness of antihistamines. Assessing the role of individual mediators in allergic rhinitis is very imprecise, but generalisations can be made (Table 1). Predictions made from this table are confirmed from clinical experience and drug trials. Antihistamines are quite effective for sneezing and itching. While rhinorrhoea is predominantly mediated through a cholinergic reflex, much of it may be triggered by a reflex mechanism involving primary mediators such as histamine. Apparently conflicting data presented by Drs. R. Neclerio and P. Van Cauwenberge at this meeting show that further work in this area is required. Nasal congestion and obstruction involve many mediators and cells, and therefore it is not surprising that antihistamines tend to be least effective when used for this indication.

The availability of the new highly selective H1 antagonists that do not cross the blood-brain barrier when taken in therapeutic doses has caused a revaluation of antihistame selection (Sutherland 1989). The simplistic approach is to choose the new non sedating antihistamines always, but these compounds are quite expensive. A simple means of selection is possible by dividing antihistamines into four groups on the basis of their CNS activities (Table 2). The clinician can then choose only one or two drugs from each group and become familiar with them.

Table 2 Antihistamine selection according to sedative effects

Sedative effect	Drug
Highly-sedative Use when sedation required	*Phenothiazine agents* eg promethazine; trimeprazine
Often sedative (perhaps 20% > placebo effect)	*Older antihistamine agents* eg brompheniramine; chlorpheniramine; clemastine; dexchlorpheniramine; diphenhydramine; diphenylpyraline; mepyramine; triprolidine
Occasionally sedative (6% > placebo effect)	eg azatadine, mequitazine
Non-sedative (sedation at placebo rate of 6%)	*New highly-selective compounds*, eg astemizole; cetirizine; loratadine; terfenadine

Symptomatic treatment with decongestants and anticholinergic agents has already been reviewed. Indications for their use are limited, but they are highly effective when employed appropriately. There has probably been an over reaction against the abuse of topical nasal decongestants: newer compounds carry a lower risk of habituation, and are extremely useful for the relief of acute symptoms of obstruction and congestion.

Mast cell stabilisation is an attractive option, but as has already been observed, newer agents have not been demonstrated to have better clinical efficacy than cromoglycate. Cromoglycate is effective in allergic rhinitis, but its usefulness is limited by the need to use it as often as every three hours. With the exception of ketotifen, which has "antiallergic" properties including inhibition of passive cutaneous anaphylaxis, antihistamines have only been shown to stabilise mast cells of concentrations above those achieved following oral administration of standard doses (Massey et al 1990).

The other therapeutic option is corticosteroids, which in their topical (intranasal) form have major advantages. They are active at every stage of the allergic reaction, even, by virtue of their anti-inflammatory properties, after mediator release has occurred. Again drawing from experience in the lower airways, where inhaled corticosteroids reduce bronchial hyperresponsiveness, it is possible that long term use of intranasal steroids may actually alter the natural history of allergic rhinitis. We now have the luxury of considering which intranasal steroid to use. Aqueous based metered dose pump sprays offer an alternative to the aerosol sprays. Apart from addressing environmental concerns about chlorinated fluorocarbons, pump sprays may achieve better drug delivery, and their wetting action may of itself produce symptomatic relief. The new, sniff activated budesonide spray now offers a further alternative.

The long term safety of intranasal steroids needs re-examination because of increasing use of high dose inhaled steroids in bronchial asthma. In a recent study by Wolthers and Pederson (1991), linear growth of the lower leg was temporarily slowed in children receiving 800 micrograms of budesonide per day (as reported by Wolthers (1991). In higher doses the lower systemic effects reported with budesonide may become clinically relevant (Johansson 1982). The newer topical steroids such as fluticosone may offer a further reduction in systemic effects (Meltzer 1990), although they are very expansive.

In summary, it is likely that the complete blocking of the allergic response by pharmacological means is neither possible nor desirable. Allergen avoidance, symptomatic treatment, mast cell stabilisation and immunotherapy all have important but limited roles. H_1 histamine

antagonists are often the drug of first choice, but there are many mediators other than histamine generated by the allergic response. The development of antagonists to other mediators will be of interest, but their very number will limit their clinical usefulness. Intranasal corticosteroids influence the whole of the allergic reaction and have probably been under utilised in the past. In particular, more information is needed on their prophylactic use (e.g. pre-seasonally) and on their possible role in modifying the natural history of allergic rhinitis.

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Topical Use of Antibiotics for Paranasal Sinusitis

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INTRODUCTION

When performing nebulizer therapy to treat paranasal sinusitis and deciding on what sort of drug to use, a variety of conditions must be considered, in addition to the problems of antimicrobial activity against individual bacteria and antibacterial spectra. We feel that aminoglycoside, fosfomycin (FOM) and cefmenoxime (CMX) are superior to other drugs as antimicrobial agents fulfilling these conditions in terms of mucosal irritation, bitter taste, antigenicity and safety. In this study we investigated the trends in the isolation of bacteria from chronic paranasal sinusitis and the usefulness of DKB, as an aminoglycoside, FOM as a fosfomycin, and CMX as a cefem, in its treatment.

MATERIALS AND METHODS

1. CMX (Cefmenoxime), an excellent anti-bacterial agent against causative agents of paranasal sinusitis, was employed in this study. Nebulization using 1% CMX solution was performed against cases which Caldwell-Luc operation were indicated and concentration of CMX at nasal mucosa, paranasal mucosa, and serum were detected to observe the distribution of CMX at these sites and also compared MIC of the main causative agents.

2. The diagnosis of chronic sinusitis was made according to symptoms, signs and radiographic findings. Two hundreds and eight patients with mild chronic sinusitis were treated with nebulizer therapy in order to determine the optimal dose of DKB, FOM and CMX. We divided the patients into 7 groups, DKB 5 mg, 10 mg, 20 mg, and FOM 30 mg, 50 mg, and CMX 20 mg, 40 mg, adjusting each of them to a total volume of 1ml of physiotogical saline solution. We performed nebulization therapy using ultrasound-type inhaler, treating the patients with an atomized dose of 0.5 ml/min, 2 min each time, 3 times a week.
Making an 8 week course of therapy, we evaluated their clinical efficacy, improvement of x-ray findings and bacteriological effect. In this period, other agents which might affect the outcome were not used in combination.
Evaluation was performed by scoring subjective and objective symptoms according to severity, and degree of improvement was determined on a 4-step scale as excellent, good, fair and poor.

RESULTS

1. The mean concentration of CMX was 0.4 μg /g at maxillary sinus (anterior wall mucosa), 1.0 μg/g at maxillary sinus (aperture mucosa), 10.8 μg/g at inferior nasal concha, 25.9 ug/g at middle nasal concha.
CMX yielded higher concentrations of nasal mucosa and maxillary sinus than the MICs against isolated organisms. (Fig. 1)

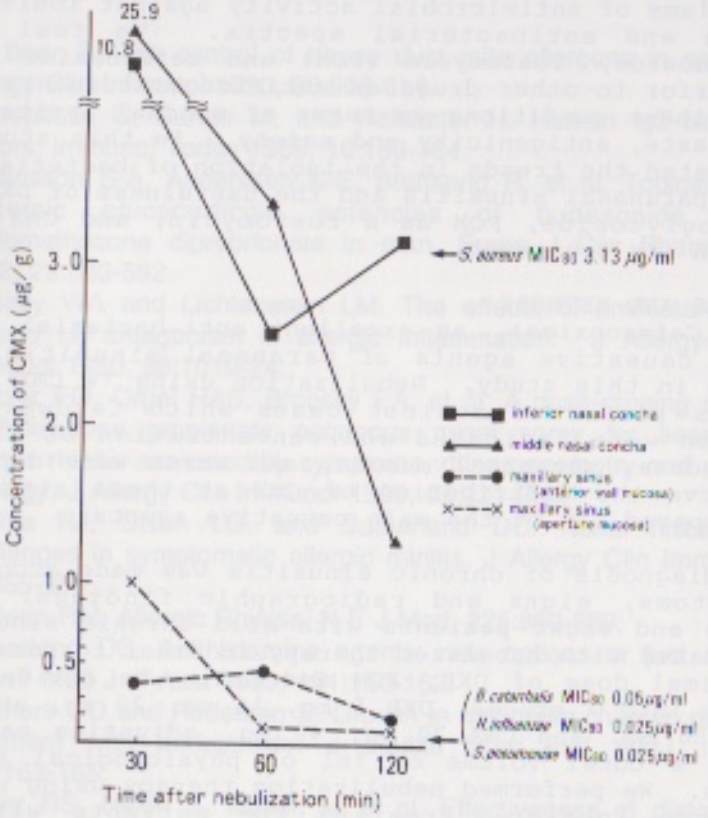

Fig. 1

2. We found that the efficacy rate, the clinical efficacy was "excellent" and "good", increased from 50% to 62% as the dose of DKB from 5 mg to 20 mg, showing increases in efficacy rate as the dose of the drugs increased. In the case of FOM, the efficacy rate was 43% at 30 mg, 71% at 50 mg. Moreover, the clinical efficacy of CMX could be expected, and the efficacy rate was 58% at the 20 mg dose, 72% at the 40 mg dose. Respectively, there was a fair degree of difference in efficacy corresponding to the dose of the drugs. (Table 1)

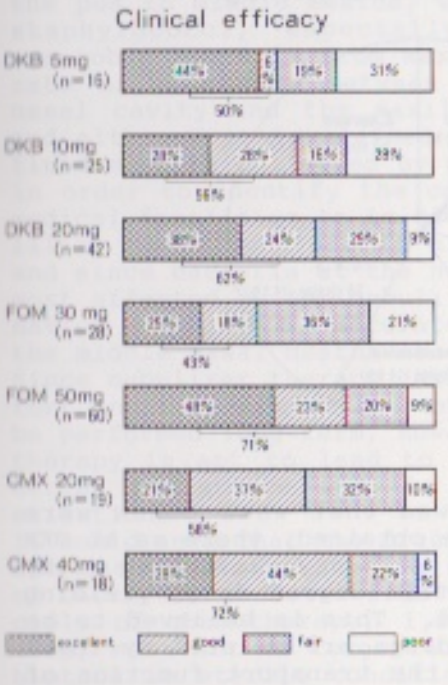

Table 1

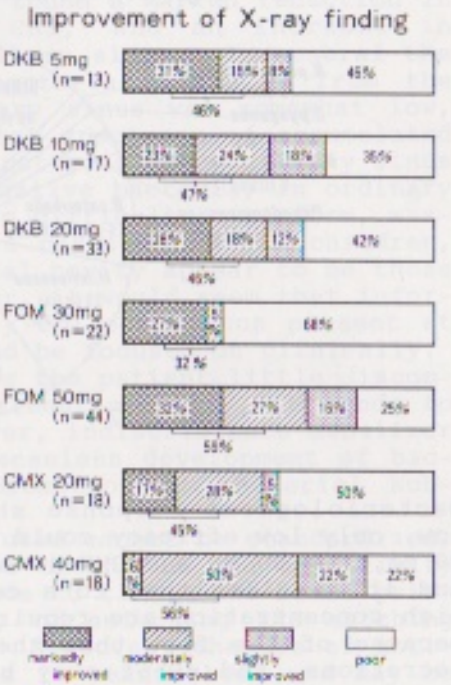

Table 2

We uniformly evaluated the improvement of X-ray findings among the patients X-rayed before and after the start of treatment and found that degree of improvement based on the X-ray findings was worse than based on the clinical findings, that in the case of the DKB group it ranged from 46% to 47%, and bearing no relation to the dose. In the case of FOM the rate was 32% at 30 mg versus 59% at 50 mg which represented the highest improvement rate. In the case of CMX the rate was 45% at 20 mg and 56% at 40 mg. (Table 2)
We conducted bacteriological studies on pus in middle nasal meatus before and after treatment. Among the 228 bacterial cultures of middle nasal meatus pus, 40 cases

(17.6%) were bacterial negative, a single strain was isolated in 163 cases (71.8%), and multiple strains were isolated in 25 cases (11.0%). By species, Staphylococcus aureus was present in 24.7% and CNS in 16.8%, with staphylococci accounting for the majority, followed by pneumococci, Haemophilus influenzae, and Branhamella catarrhalis. Anaerobic bacteria consisted of just 6 strains of anaerobic streptococci equivalent to 2.6% of the isolates. (Fig. 2)

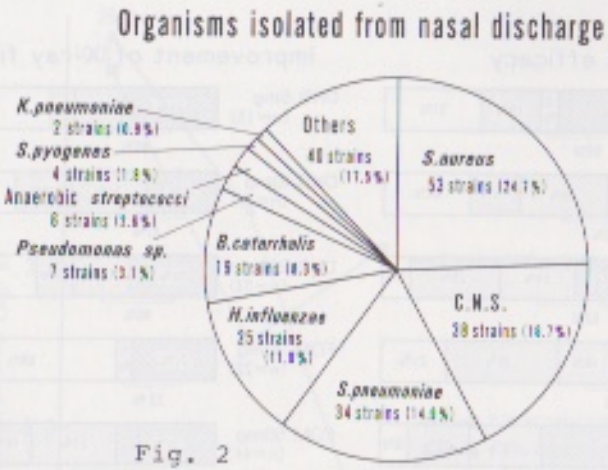

Fig. 2

Bacteriological response showed that when doses were low, only low efficacy could be obtained, where as at DKB 20 mg, FOM 50 mg and CMX 40 mg, efficacy was rather high, and it is clear that to a certain degree doses yielding high concentration are required. This is believed to be because of the fact that the drugs are diluted by local secretions, and swept away by the transport function of mucosal cilia, and so forth, making it impossible for the drugs to perform efficaclously at low concentrations.

DISCUSSION

One of the causes of paranasal sinusitis is bacterial infection, and therefore, drug used in nebulizer is mainly antibiotics. Among the antibiotics, aminoglycosides are frequently used due to its stability in aqueous solution, its property of being tasteless and odorless with less stimulation to mucosa, and also due to its low antigenicity. On its demerit, however, lies in its poor efficiency against pneumococcus and anaerobic agents. We therefore, performed nebulization treatment using FOM and CMX which are both fit as nebulizer solution and also has broad spectrum as antibiotics. The receptive results were compared to that using DKB as an aminoglycoside.

Based on the results of the concentration of CMX at nasal mucosa and paranasal mucosa, it appears that the efficacy of the nasal nebulizer depends on indirectly improving maxillary sinus lesions by controlling inflammation at the nasal cavity and improving mucosal edema rather than by directly improving the lesion at the maxillary sinus itself. So even the antibacterial effect of a drug is weak, when drugs which have a considerably better bacterial MIC are administered directly, a certain degree of efficacy can be anticipated.

When we made a comparison with the bacteria isolated from the fluid obtained by maxillary sinus puncture and from the pus in middle meatus, we found a marked reduction in staphylococci, especially CNS, and an increase in anaerobic bacteria from maxillary sinus. In general the rate of agreement between bacterial isolates from the nasal cavity and the maxillary sinus was somewhat low, and although it is claimed that specimens of accumulated fluid must be collected by puncturing the maxillany sinus in order to identify the causative bacteria, in ordinary medical facilities it is often difficult to perform, maxillary sinus puncture in mild cases and small children, and since bacteria at the nasal cavity appear to be those most affected by the nebulizer, it would seem that information obtained by accurately collecting pus present at the middle nasal meatus should be focused on clinically.

Since nebulizer therapy causes the patient little discomfort and is a convenient treatment modality, it tends to be performed long-term, however, indiscriminate nebulizer therapy is apt to lead to senseless development of bacterial resistance and the promotion of bacterial substitution.

It would seem that the drugs used cannot be standardized, but that after evaluating the trends in the sensitivity of bacterial isolates from time to time, the basic principle of chemotherapy, i,e., of selecting the matching drug, must not be forgotten. Moreover, the use of antibiotics in sterile conditions is meaningless and may be accompanied by the development of adverse effects. Consequently, drug selection must be performed after adequately determining the patient's status and making one's choice while checking the degree of improvement in clinical symptoms.

CONCLUSION

The antibacterial activity of FOM and CMX investigated in this study is relatively broad and they also meet the conditions required of a nebulizer solution. So they appear to be highly useful drugs for nebulizer therapy.

Chairman's Introduction

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The nose has many functions. The most well-known function is of course ventilation. Since many years ventilation can be measured by rhinomanometry and since 1983 rhinomanometry has been standardized so that the results of different centers can be compaired.

The Standardization Committee decided that active anterior rhinomanometry should be the method of choice to measure nasal ventilation. It is a well-known fact that the use of nozzles to measure the naso-pharyngeal pressure, gives a distortion of the nasal vestibulum and therefore its use must be avoided. Still according to the Standardization Committee the best technique to get an air-tight seal with minimal distortion of the nostrils is the adhesive tape technique. To measure the nasal airflow, the use of a mask is prefered. Any type of mask that does not result in deformation of the nose and does not give leaks is acceptable. Furthermore, a nask should be transparant so that eventual deformation of the nostrils or kinking of the tubing can be excluded.

Furthermore the equipment must be calibrated regulary. The International Standardization Committee has a workgroup that is actually discussing a calibration technique by means of an "artificial nose". The recording should always be performed during quiet breathing, unless the patient does not reach a flow of 300 cm^3 sec^{-1}. The patient should be in the sitting position and have a restperiod of at least 30 minutes before the actual rhinomanometry.

The XY recording was considered to be the best way of recording because it shows very well the relationship between pressure gradient and flow. The graphic mirror image presentation is by now well known worldwide. It was unanimous decided that rhinomanometric values should be expressed in SI units (pressure in Pascal and flow in cm^3 sec^{-1}). Preference should be given to the expression of the resistance at the fixed pressure rather than at the fixed flow. The reference pressure was determined at 150 Pascal. For those using the Broms' mathematical model, the expression of the resistance at radius 200 in a polar coordinate system was considered to be equally good. Although all committee members were aware of the fact that the equation was not fully correct, they accept the equation $R = \Delta p/\dot{V}$. It was also recommended that for a reliable measurement a minimum of 3 to 5 breaths should be recorded and averaged. Later it appeared that a pressure of 150 Pascal during quiet breathing can be reached easily by patients but not by test subjects in a normal population. Therefore, the Standardization Committee allowed for anterior rhinomanometry the elaboration of the resistance at the following pressure values i.e.: 75, 100 and 150 Pascal. The use of drugs or nasal valve dilatators should be mentioned on the graph.

The aim of rhinomanometry of course is to study nasal ventilation and to determine the degree of obstruction. The sensation of nasal obstruction, however, does not always correlate with the rhinomanometric data. Bachmann in 1983, studied the correlation of nasal resistance with anterior rhinoscopy and the history of the patient. He found that in 75 % there existed an immediate correlation or a 100 % correspondence between the 3 parameters after re-evaluation. In 5% there existed a good correspondence between the history and rhinomanometry, in 11 % between history and rhinoscopy and in another 5% between the history and inspection. In only 4 or 5 % there was no correspondence between those 3 parameters.Clement et al. (1983) compared postoperative parameters of the Broms'model with the complaints of the patients. Twenty three out of the twenty six patients were satisfied after the operation. Rhinomanometry showed in 70 % a clearcut improvement and in 30% only a moderate improvement. Three patients complained of unilateral insufficient nasal passage after surgery and this was confirmed by rhinomanometry. It appears from this study that rhinomanometric data in fact are more reliable than the subjective feeling of the patient. Furthermore, it is also obvious that the correspondence between the parameters of a mathematical model and the complaints of the patient are far better than the correspondence between the resistance at 150 Pascal and the complaints. This is not amazing because a mathematical model describes the recording completely while the resistance value at a pre-determined pressure only describes one point of the whole recording. By using different chemical substances, the sensation of nasal airflow can be influenced but this phenomenon has been studied extensively by Eccles and the results will be presented by the author.

It is the opinion of the author that in rhinoplastic surgery the results must not only be evaluated by pre-and postoperative photography but should also include an objective test of nasal ventilation. The most appropriate investigation to test this nasal ventilation is rhinomanometry. The author was able to show, by using a mathematical model, that postoperative results always showed an improvement of the rhinomanometric data. When comparing, however, the postoperative data with the data of a normal population, it was obvious that the normal average values cannot be achieved by surgery. Most mathematical models described a complete recording by means of two parameters. These parameters are ideally suited for statistical analysis and learns the rhinosurgeon to be more modest about his results.

By now it is clear that mathematical models are more superior in describing the rhinomanometric recording than only nasal resistance at a predetermined pressure. The use of these models as well as the necessity of averaging several recordings in one patient make

the use of computers in rhinomanometry necessary. Many different models have being studied for the first time by Pallanch (1984) and later by the author. By using computerized rhinomanometry, it is possible to compare the reconstructed recording using the mathematical model with the actual recording. The study demonstrated that the polynomial model of Rohrer and the polar coordinate model of Broms are the 2 best models actually available. They both describe the real recording with great precision. By using a Fournier analysis, the author determined the optimal sample frequency necessary in computerized rhinomanometry. By testing 100 test subjects, a sample frequency of 50 Hz proved to contain as an average more than 90% of the information of the recording. Another advantage of computerized rhinomanometry is the possibility to determine the distribution in a normal population (test subjects without complaints of nasal blockade). From this study it was clear that to obtain a normal distribution of the rhinomanometric data, rhinoscopy must be included in the selection criteria of normality. When studying the same population of 100 test subjects before and after decongestion, it was clear that as an average 97% of the subjects could reach 75 Pascal during inspiration in the non-decongested nose and 86% of the population during expiration. In the decongested nose 94% could reach 75 Pascal during inspiration and only 74% during expiration. This is one of the reasons why the Standardization Committee included 75 Pascal and 100 Pascal when using normal populations. When using the whole population, the cumulative frequency distribution of resistance showed normal distribution after decongestion and also for the total nasal resistance as well before as after decongestion. When studying the subgroups of these 100 test subjects (i.e. subgroup 1: patients with no nasal complaints and a normal rhinoscopy and subgroup 2 : patients with no complaints but the presence of slight anatomical anomalies by rhinoscopy) it was clear that the distribution of subgroup 1 was practically normal as well after decongestion as before decongestion while for subgroup 2 the distribution was only normal after decongestion. All this demonstrates the need of computerized rhinomanometry and this will be further discussed by Pallanch. The influence of decongestion and exercise on rhinomanometry will be presented by Hasegawa. In recent years a new technique to study the geometry of the nose has been introduced by Grymer et al. (1989). They called the technique acoustic rhinometry and unfortunately have compared the data of this technique with the rhinomanometric data. Unfortunately because both techniques measure completely different properties of the nose. Rhinomanometry studies the ventilation function of the nose and is a dynamic study. It is not fit to evaluate the cross-sectional areas of the different stenotic areas in the nasal airway. Acoustic rhinometry is a static study of the geometry of the nose and is in fact an imaging technique also with advantages and disadvantages. Its value, however, should only be compared with other imaging techniques such as CT-scan and MRI. Pirsig has a great experience with the technique and will discuss its usefullness in the diagnosis of ronchopathy.

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Nasal Airway Resistance and Nasal Sensation of Airflow

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INTRODUCTION

The sensation of nasal airflow is important in clinical practice as it is the symptom of nasal obstruction rather than a change in nasal airway resistance which most frequently causes patients to present for treatment. It is not generally appreciated that nasal obstruction as a symptom is primarily related to the sensation of nasal airflow perceived by the patient, rather than a functional change in the ability to breathe through the nose.

The trigeminal nerve supply to the nose mediates the sensation of nasal airflow via the innervation of the nasal vestibule and nasal mucosa (1,2). There is now good evidence that this sensation is mediated via trigeminal thermoreceptors as inhalation of L-menthol causes an increased sensation of nasal airflow. The subjective sensation of nasal airflow is only one component of the trigeminal nerve input, as respiratory control is also influenced by nasal airflow (3,4).

SENSATION OF NASAL AIRFLOW

The subjective awareness of respiration and the regular respiratory rhythm comes primarily from stimulation of nasal sensory receptors rather than from lung stretch receptors or proprioceptors in the respiratory muscles. Each inspiration draws air through the nasal passages and this air stream stimulates cold receptors in the nose and provides the regular cool sensation of normal breathing.

It is not known which area of the nose is most important for the sensation of nasal airflow. The nasal valve is strategically placed at the entrance of the nasal cavity and the inspired air velocity is maximal at this point as this section forms the smallest cross sectional area of the whole respiratory tract. A cooling stimulus from the inspired air would be maximal at the level of the nasal valve and there is experimental evidence that local anaesthesia of this area either by local injection or topical application of anaesthetic causes a decrease in the sensation of nasal airflow (5,6). However the nasal

mucosa also appears to sense nasal airflow, as topical anaesthesia of the mucosa has been shown to influence sensation of nasal airflow (7,8).

The measurement of nasal sensation of airflow is entirely subjective and involves the patient in scoring how they 'feel'. The visual analogue scale which consists of a 10 cm line on which the subject scores their sensation has been successfully used in studies on nasal sensation of airflow involving the effects of menthol and nasal anaesthesia (7,9). The visual analogue scale looks deceptively simple as a research tool, but great care must be taken in labelling the scale and in the instructions given to subjects as it is very easy to unintentionally bias the results.

FACTORS THAT INFLUENCE NASAL SENSATION OF AIRFLOW

The integrity of the trigeminal sensory nerves supplying the nose is essential for the normal sensation of airflow. Damage to the nasal valve area and nasal mucosa can cause a sensation of nasal stuffiness despite the fact that the nasal resistance may be unchanged or even decreased. Damage to the nasal mucosa as occurs with atrophic rhinitis or with diathermy and cryotherapy may cause a sensation of nasal stuffiness despite a decrease in nasal resistance to airflow.

Nasal anaesthesia has been shown to decrease the sensation of nasal airflow without any change in nasal airway resistance (5,6,7).

Menthol is widely used for the treatment of nasal congestion associated with upper respiratory tract infection but experiments have demonstrated that menthol increases nasal sensation of airflow without any effect on nasal resistance to airflow. The effects of ingestion of a menthol lozenge on nasal sensation and airway resistance are illustrated in Fig. 1. Inhalation of menthol vapour has the same effects as the lozenge (1,9,10). It is believed that menthol has a specific sensitising and stimulating action on nasal cold receptors which causes an increased sensation of nasal airflow without any change in nasal airway resistance.

Studies on the D and L isomers of menthol indicate that L menthol has a specific pharmacological action on nasal sensory receptors as the D isomer is much more biologically active than the L isomer (1).

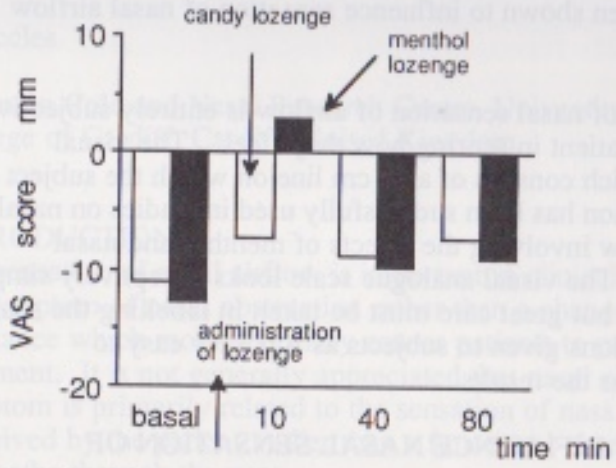

Fig.1. The effects of administration of a lozenge containing 11mg menthol (shaded bars) and candy placebo lozenge (unshaded bars) on Visual analogue scores (VAS). The scores for VAS were measured from the midline of a 100 mm scale with 0 to -50 mm towards the side marked " nose feels extremely blocked" and between 0 and + 50 mm towards the side marked "nose feels extremely clear." There was a significant difference between basal and 10 min post dosing scores in the menthol group ($p<0.0001$), and between the placebo and menthol groups at the 10 min post dosing time($p<0.05$). The results represent the means (+/- sem, n = 30 for placebo and 32 for menthol group). Basal VAS scores were taken immediately prior to dosing with the lozenge and the times (10,40,80 min.) are given as those after dosing. From Eccles, Jawad and Morris ,1990 (9)

RELATIONSHIP BETWEEN NASAL AIRWAY RESISTANCE AND NASAL SENSATION OF AIRFLOW.

Subjects with an increased nasal airway resistance related to acute upper respiratory tract infection complain of nasal congestion but recent studies have shown that there is no relationship between the objective and subjective measurements of nasal obstruction. This indicates that other factors apart from nasal airway resistance influence the sensation of nasal airflow. Oedema or inflamation around the sensory nerve endings in the nasal mucosa may disturb sensory nerve function and create a sensation of nasal obstruction in subjects with acute upper respiratory tract infection. Congestion of the nasal mucosa in areas away from the nasal valve may create a sensation of nasal stuffiness and obstruction without any influence on nasal airway resistance as the congestion would be outside the main path of nasal airflow.

SUMMARY

Nasal obstruction is a common symptom which is most frequently associated with an increased nasal airway resistance. However it is important to appreciate that the objective measurement of nasal airway resistance does not always correlate with the subjective perception of the degree of nasal obstruction. Damage to trigeminal sensory nerve endings can cause a sensation of nasal stuffiness without any change in nasal airway resistance and similarly inhalation of menthol can cause a subjective improvement in nasal sensation of airflow without any change in nasal resistance.

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Clinical Application of Computerized Rhinomanometry

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INTRODUCTION

Rhinomanometry has found an established role in the laboratory. It has also been found to be worthwhile by some clinicians in allergy challenge testing and in pre- and post-op evaluations. Controversy exists, however, regarding how useful rhinomanometry can be in the typical clinical setting for the evaluation of the patient with the symptom of nasal obstruction. Some clinicians feel that the patient's description of symptoms is the best means of assessing obstruction and that airway studies are not helpful. Some investigators have stated that there is no correlation between nasal resistance and the symptom of nasal obstruction.

When rhinomanometry is used, the clinical evaluation of the patient entails an integration of the patient's symptoms, history and nasal airway study results. In order to establish the validity of using rhinomanometry in the clinical setting it must be shown to yield results that correlate with symptom and examination findings yet sometimes provide additional information that enhances the diagnostic process.

MATERIALS AND METHODS

We evaluated a group of patients who had unilateral intranasal pathology and unilateral symptoms. Anterior mask rhinomanometry was used in the same way that we have previously described (Pallanch et al, 1985). Between 1983 and 1989, 2,633 patients were studied using computerized rhinomanometry at the Mayo Clinic. Of these, 2,316 complained of nasal obstruction. Intranasal pathology had been entered and stored in the computer for 679 of these patients. The most straight forward symptom to examine is the side of obstruction. For this it was necessary to exclude those patients who did not have both unilateral pathology and unilateral symptoms. In addition, patients were excluded who had polyps, synechiae, or septal perforations. The patients were studied as groups with the pathologic types: valve area, septal and valve and septal. Patients with other intranasal pathology were excluded. This left 57 patients with right sided pathology and 63 patients with left sided pathology. None of these patients had any documented mucosal or turbinate hypertrophy. We tabulated the instances of correspondence between the side of the symptoms, the side of the pathology, and the side of greatest nasal resistance (at a radius of 2, Broms, 1982; Clement, 1984).

We also looked at the group of patients with documented mucosal and/or turbinate pathology. After excluding those with polyps, synechiae and septal perforations, there were 149 patients with documented mucosal and/or turbinate pathology, many of whom also had valve and/or septal pathology. Of these, 33 had right sided and 30 had left sided unilateral mucosal and/or turbinate pathology. From this group we selected those with valve/septal pathology only on the side opposite the unilateral mucosal/turbinate pathology. This left 13 patients with unilateral symptoms.

RESULTS

The overall relationship of the three factors (side of symptoms, side of noted pathology, and side of highest nasal resistance) are shown for studies done before (Fig. 1) and after (Fig. 2) decongestion of the nose. Table 1. shows a summary of the results listing percentage of patients for each type of relationship of symptoms, pathology and airway data for each of the pathology groups and for all the groups combined.

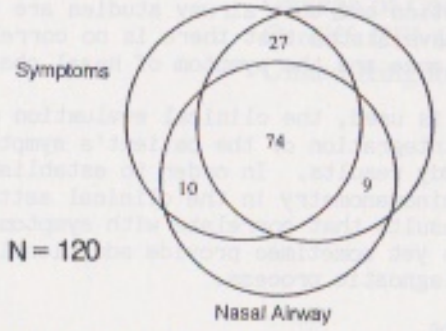

FIGURE 1. Patients with only unilateral valve or septal or valve and septal pathology. Compared with: side of symptoms (right, left) and airway measurement BEFORE decongestion.

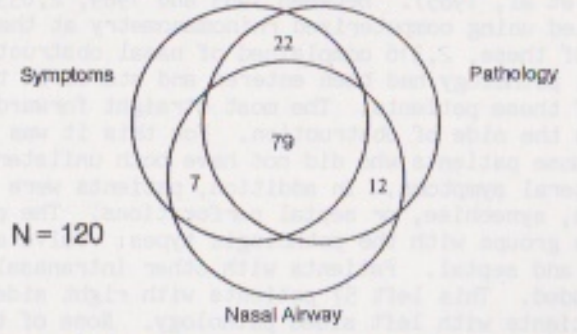

FIGURE 2. Patients with only unilateral valve or septal or valve and septal pathology. Compared with: side of symptoms (right, left) and airway measurement AFTER decongestion.

Patients with Unilateral Pathology				
Before Decongestion	Valve	Septal	Valve Septal	Total Avg.
SX = PX = RN	57%	61%	68%	62%
(SX = PX) ≠ RN	21%	19%	29%	23%
SX ≠ (PX = RN)	12%	9%	0%	7%
(RN = SX) ≠ PX	10%	11%	3%	8%
After Decongestion	Valve	Septal	Valve Septal	Total Avg.
SX = PX = RN	66%	45%	91%	66%
(SX = PX) ≠ RN	14%	32%	6%	18%
SX ≠ (PX = RN)	10%	16%	3%	10%
(RN = SX) ≠ PX	10%	7%	0%	6%

TABLE 1

Fig. 3 shows the correspondence of the side of symptoms, side of valve/septal pathology, and side of highest resistance for the 13 patients with documented mucosal and/or turbinate pathology. In 11 of the 13, the symptoms matched the side of the valve/septal pathology. The side of highest resistance often corresponded and did so best after decongestion.

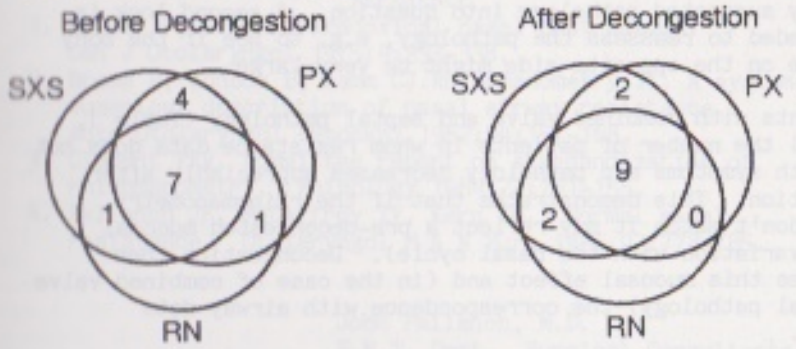

FIGURE 3. Patients with documented unilateral valve and/or septal pathology with opposite side turbinate/mucosal pathology. 13 had unilateral symptoms. Symptoms were worst on the side of valve/septal pathology in 11 of 13.

DISCUSSION

In patients with unilateral valve/septal pathology the side of symptoms, pathology and highest resistance corresponded 62% of the time before decongestion and 66% of the time after decongestion. This demonstrates that nasal airway data does correlate with nasal symptoms and intranasal pathology a significant portion of the time. This lends validity to the use of rhinomanometry to study nasal breathing function.

The side of symptoms and pathology but not the site of highest resistance corresponded 23% of the time before decongestion and 18% of the time after decongestion. When the airway measurement result is different than expected from the symptoms and examination, a second look is warranted to identify the cause of the greater airway restriction. This offers the potential of revealing pathology that wasn't initially evident to the clinician. This is information that wouldn't have been evident without the rhinomanometric study.

The side of pathology and highest resistance corresponded but the symptoms were on the opposite side for 7% of patients before decongestion and for 10% after decongestion. The rhinomanometry results verify that the side of the pathology is most restricted in this otherwise contradictory situation. This appears to demonstrate the phenomenon of paradoxical nasal obstruction (Arbour 1975). In such cases the rhinomanometric results help to clarify conflicting clinical data (symptoms and examination findings).

The side of symptoms and highest resistance corresponded but the pathology noted was on the opposite side for 8% of patients before decongestion and 6% after decongestion. Again we have conflicting clinical data. The resistance is highest on the side of the symptoms. This brings the relative significance of the initially suspected pathology into question. A second look is again needed to reassess the pathology, e.g. to see if the bony turbinate on the opposite side might be very large.

In patients with combined valve and septal pathology (Table 1, Column 3) the number of patients in whom resistance data does not agree with symptoms and pathology decreases appreciably after decongestion. This demonstrates that if the rhinomanometry results don't match it may reflect a pre-decongested mucosal status (variation with the nasal cycle). Decongestion then eliminates this mucosal effect and (in the case of combined valve and septal pathology) the correspondence with airway data improves.

In the patients with unilateral mucosal/turbinate pathology, even though the side of the symptoms and the side of the valve/septal pathology matched, the nasal resistance was still higher on the turbinate side 36% (4 of 11) of the time before decongestion and

18% (2 of 11) of the time after decongestion. This again shows a situation can occur in which resistance data can reveal the actual most restricted side (turbinate hypertrophy side) of the airway when the patient's symptoms may have caused us to turn our attention to the septal pathology.

Though it is not the most frequent situation, the turbinate/mucosal pathology on the opposite side can play a role and needs to be considered when the symptoms or resistance data don't correspond to the valve/septal side.

Additional complexity results if consideration is also given to: bilateral symptoms, degree of symptoms, bilateral valve/septal pathology, effect of other areas of pathology, degree of pathology symptoms at the time of test vs. usual symptoms, and symptoms before and after decongestion. It was necessary, however, to examine a simpler more understandable group of cases to check the validity of the clinical use of airway testing results.

We've demonstrated that nasal airway data does correlate with symptoms and nasal pathology. We've also shown that there are a significant number of cases in which rhinomanometry could help to delineate the nature of the problem in patients with the symptom of nasal obstruction.

The presence of a correlation between nasal symptoms, pathology, and test results gives validity to further study of the complex relationships of these factors with the goal of optimal clinical assessment and choice of therapy for the patient who experiences nasal obstruction.

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Clinical Significance of Rhinomanometric Changes Induced by Exercise and Decongestants

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INTRODUCTION

Nasal obstruction is a very important and common symptom of patients suffering from nasal disorders. Therefore, it is extremely important to objectively evaluate nasal obstruction in such patients. Rhinomanometry is a useful method to evaluate nasal obstruction by means of measuring nasal resistance. However, nasal resistance is not invariable. In particular, unilateral nasal resistance, the nasal resistance of each side of the nose, changes alternately from time to time. This phenomenon is called the nasal cycle. In addition to this spontaneous alternate changes, nasal resistance is affected by other factors such as exercise, changes of temperature and humidity, posture, hyperventilation, breath holding or psychic stress. Intranasal spray of decongestants also alters nasal resistance.

The change in nasal resistance is mainly caused by congestion and decongestion of the nasal mucosa. Dynamic changes of nasal resistance induced by exercise or decongestants reveal responsiveness of the nasal mucosa. Evidence suggests that there is difference in nasal responsiveness between normal subjects and patients with allergic rhinitis.

The aim of this study is to evaluate the nasal response induced by exercise or decongestants for better understanding the pathophysiology of allergic nasal mucosa on clinical basis.

MATERIALS AND METHODS

Exercise

Four groups were used in this study: 30 children with bronchial asthma(17 males and 13 females, 6-14 years of age), 7 normal children(2 males and 5 females, 8-9 years of age), 90 adult patients with allergic rhinitis(39 males and 51 females, 16-38 years of age) and 26 normal adults(16 males and 10 females, 17-31 years of age). The first two groups were investigated to determine the changes in FEV1.0 and nasal resistance induced by exercise, and the other two groups were investigated to determine the changes in nasal resistance.

A 6-minutes fixed-load treadmill exercise was used in this study. The subjects were forced to walk about 6 km/hr for 6 minutes on a treadmill.

In children groups, FEV1.0 and nasal resistance were measured by spiroanalyser CSA 800(Fukuda, Japan) and Rhinorheograph(Nihon-Koden), respectively. FEV1.0 was measured before exercise, 5, 10, 15, 20, 25, and 30 minutes after exercise. Right and left unilateral nasal resistance was measured by anterior rhinomanometry before exercise, immediately after exercise, 4, 9, 14, 19, 24, and 29 minutes after exercise in each subject. In the case of unilateral complete nasal blockage, nasal resistance was measured by posterior rhinomanometry. In adult groups, nasal resistance was measured before exercise, immediately after exercise, 5, 10, 15, 20, 25, and 30 minutes after exercise in the same way. All of the patients were not allowed to have any drugs during 48 hours before examination. They were examined in room air at 22-24°C. The relative humidity varied from 40-60%.

Decongestants

Twenty-eight normal subjects(12 males and 16 females, 18-54 years of age) and thirty-nine patients with allergic rhinitis(22 males and 17 females, 16-64 years of age) were investigated in this study. 0.05% Naphazoline(Privina) was used as a topical nasal decongestant, nasal spray.

The changes of nasal resistance were measured in 16 of 28 normal subjects before nasal spray, 5, 10, 20, and 30 minutes after spray. Unilateral nasal resistance was first measured by anterior rhinomanometry and then total nasal resistance was calculated. The nasal resistances before nasal spray and 20 minutes after nasal spray were compared in normal subjects and patients with allergic rhinitis.

RESULTS

Exercise

Nineteen(63%) of the 30 children with bronchial asthma who underwent exercise testing showed positive EIA(exercise-induced asthma, percent reduction of FEV1.0 > 15%), while the other 11 patients(37%) showed negative EIA. All of the 30 patients and the 7 normal children showed a marked decrease in nasal resistance immediately or 4 minutes after exercise in the more congested side of the nose. The change in nasal resistance in the less congested side of the nose was not remarkable. Nine(30%) of the 30 patients showed unilateral complete nasal blockage(exercise-induced nasal obstruction,EINO) from 14 to 19 minutes after exercise(Fig.1). None of these patients had unilateral or bilateral complete nasal blockage at the preexercise test. The other 21 patients showed negative EINO. Positive EINO was found in 7 of 19 patients with positive EIA and 2 of 11 patients with negative EIA.

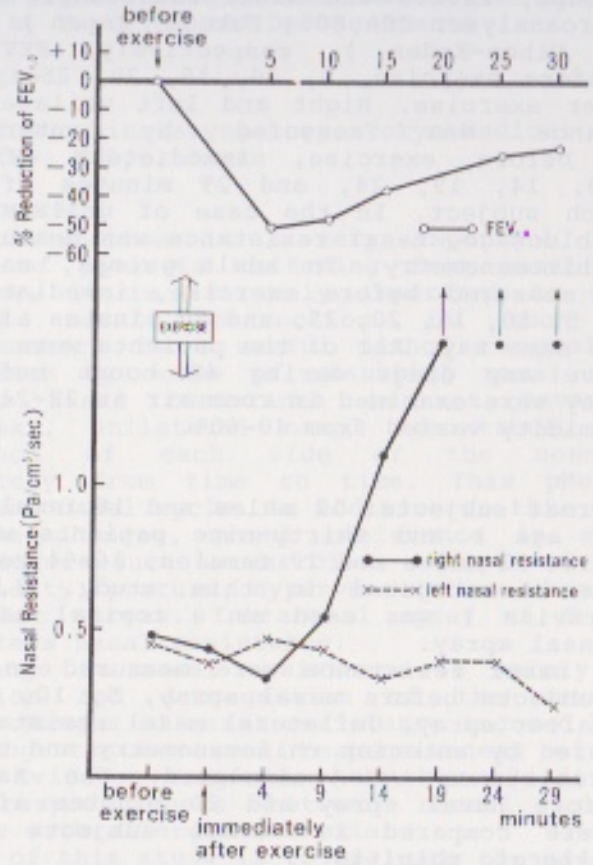

Fig.1 The change in FEV1.0 and nasal resistance induced by exercise in an asthmatic child. The maximum percent reduction of FEV1.0 is 52%(positive EIA) and unilateral complete nasal blockage is seen in the right nasal cavity(positive EINO).

None of 7 normal children showed positive EIA or positive EINO.
On the other hand, 90 adult patients with allergic rhinitis samely showed marked decreases of nasal resistance immediately after exercise. Twenty(22%) of 90 patients showed marked increase of unilateral 10-30 minutes after exercise. The normal subjects showed marked decreases of nasal resistances immediately after exercise as much as the allergic did, but none showed unilateral complete nasal blockage.

Decongestants

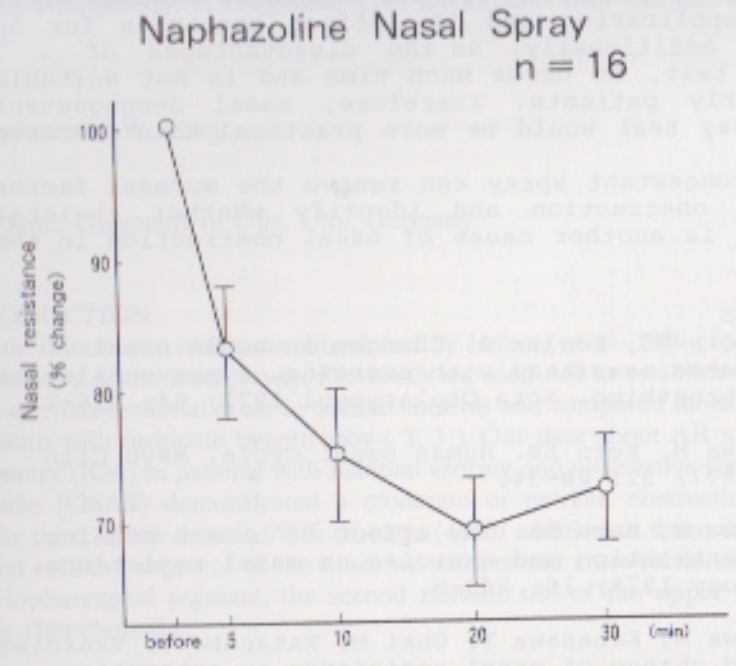

Fig.2 The maximum effect of Napahzoline nasal spray appears about 20 minutes after the spray.

Fig.2 shows the changes of nasal resistance before nasal spray, 5, 10, 15, 20, and 30 minutes after spray in normal subjects. Total and unilateral nasal resistances before nasal spray showed statistical differences between normal subjects and patients with allergic rhinitis. However, there were no statistical differences in total and unilateral nasal resistances 20 minutes after nasal spray.

DISCUSSION
Nasal obstruction is caused by pathologic swelling of the nasal mucosa and/or skeletal deformity of the nasal cavity. Exercise and nasal decongestants relieve nasal obstruction by inducing the shrinkage of the nasal mucosa. This phenomenon is found not only in patients with allergic rhinitis butalso in normal subjects. On the otherhand, exercise induces rebound phenomenon, i.e., EINO, after the cessation of exercise in 20-30% of patients with allergic rhinitis. Therefore, exercise has an advantage to see different kinds of responses during the postexercise period. However, as far as the shrinkage of the nasal mucosa is concerned, the duration of the effect is much shorter in exercise than in nasal decongestants. The maximum effect of

Naphazoline nasal spray appears around 20 minutes after topical application and the effect continues for 5-7 hours. Additionally, as the disadvantages of exercise test, it needs much time and is not suitable for elderly patients. Therefore, nasal decongestant nasal spray test would be more practical than exercise test.
Nasal decongestant spray can remove the mucosal factor in nasal obstruction and identify whether skeletal deformity is another cause of nasal obstruction in the patients.

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Acoustic Rhinometry: A Diagnostic Tool for Patients with Chronic Rhonchopathies

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INTRODUCTION

Acoustic rhinometry (AR) was introduced by Hilberg et al. 1989 (1) to assess the geometry of the nasal cavity. Previously we used AR to establish reference values of cross-sectional areas in normal controls and compared them to values of patients with turbinate hypertrophy (2, 3). Our data about AR and rhinomanometry (RM) in patients with habitual snoring and obstructive sleep apnea syndrome (OSAS) demonstrated a moderate or marked obstruction in the anterior third of the nose in 79 % of cases (4). In addition to these data about this first resistive segment of the nose, we will present cross-sectional areas of the velopharyngeal segment, the second stenotic site of the upper airway in chronic rhonchopaths.

MATERIALS AND METHODS

117 males and 3 females, aged 22 to 70 years (mean 49), were studied by ENT-examination, polysomnography, radiocephalometry, nasopharyngeal videoendoscopy, RM and AR to evaluate the severity of OSAS. All patients were studied overnight during sleep without any sedative drug or alcohol prior to these studies. Based on the respiratory disturbance index (RDI), we found 78 habitual snorers (mean RDI=6.7; range 3- 10) and 42 patients with OSAS (mean RDI= 38; range 11-82).
AR is performed by an equipment as described by Hilberg et al. (1) and modified by Lenders (2 - 4). It has a computer (IBM®-AT 486 compatible) with analog-to-digital converter, a source-generator, a wave tube (1.5 cm inner diameter, 90 cm length) and microphone with amplifier and filter. Unlike Hilberg et al. (1) we use 6 different polyphen nosepieces (inner diameter 1.5 cm, length 7 cm) with a taper opening at the nostril measuring from 0.5 to 1.1 cm outer diameter. A tight fit of the nosepiece to the individual nostril is achieved without deformation of the nasal lobule.
The source-generator produces a click that is detected by the microphone. After arriving in the nasal cavity, the click is reflected by changes in local impedance resulting from changes in the cross-sectional areas of the nasal cavity. The analog signal from the microphone is amplified, filtered, and digitized at a sampling rate of 50 kHz. The calculated data are converted to an area-distance function and displayed by area plotting on a logarithmic scale.

The equipment allows repeated measurements at up to 50 Hz and calculates optionally mean curve and standard deviations of these repeated measurements. Ten curves in each different state (before and after decongestion, right and left sides separately) are automatically recorded. Superposition of different curves is used for evaluation and documentation. All measurements of AR and RM were performed on awake subjects in a seated position during normal breathing. For evaluation of the velopharyngeal segment, we use the mean curves with standard deviations (SD) of the measurements of the wider decongested nasal cavity. Our new equipment and software allow RM measurements with the same hard and software. The RM measurements in this study were performed as an active computerized anterior RM according to the evaluation method described by the International Committee on Rhinology. To study the influence of nasal mucosa, patients were measured by AR and RM before and 15 minutes after decongestion with 0.5% tramazoline hydrochloride. This test was performed by spraying the solution into the inferior and middle nasal meatus. To study different cross-sectional areas in the velopharyngeal segment by acoustic rhinometry, investigations on models of nasal cavities with various shapes, sizes and positions of the velum were undertaken. The nasal models were taken from human cadaver, built up with wax and outlined with sticky wax.

Previous studies showed a limitation of AR. When measuring very small cross-sectional areas in the nasal cavity there is a value below which measurements behind this very small cross-sectional area become incorrect. This critical value of a stenosis is a relative value, which depends on the size of the nasal cavity behind this first stenosis and on the distance of another measured cross-sectional area behind the first stenosis. This critical value seems to be 0.4 cm^2 in adults.

RESULTS

ACOUSTIC RHINOMETRY IN NORMAL CONTROLS

Figure 1 shows the mean curve with standard deviations of a 53 year old man, representative for our normal control group after decongestion. The first centimeters (straight line) of the curve reflect the dimensions of the nosepiece and allow a self-test of the system. The first notch of the curve (Isthmus nasi notch = I - notch) represents the minimal cross-sectional area with 0.73 cm^2 at 1.1 cm distance from the nostril, corresponding to the isthmus nasi (valve region).

The second notch (Concha inferior notch = C-notch) with cross-sectional area of 1.21 cm^2 at 3 cm corresponds to the head of the inferior turbinate and the anterior part of the septal concha.

This pattern of curve - we term it a "climbing W" pattern - with the minimal cross-sectional area at the isthmus nasi and a second minimum at the region of the anterior inferior turbinate was observed in all normal controls. The intraindividual variability of the cross-sectional areas in the nasopharyneal segment is represented by the standard deviations of repeated measurements in the last 4 centimeters of the curve. In the normal control group we found standard deviations in the velopharyngeal segment not larger than 16 % of their mean values.

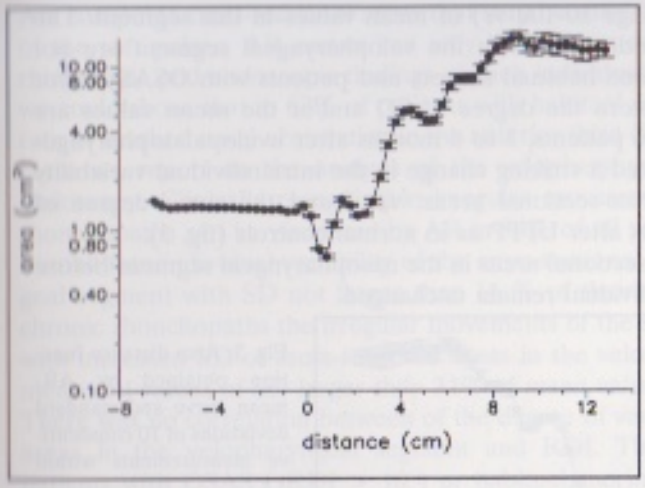

Fig. 1: Area distance function obtained by AR; mean curve and standard deviations of 10 measurements within 3s of the right nasal cavity 15 min after decongestion. Example for normal control (male, 53 years without nasal complaints): SD in the velopharyngeal segment is less than 16% of mean values.

Fig. 1 shows standard deviations in the velopharyngeal segment that range between 10% and 15% of their mean values.

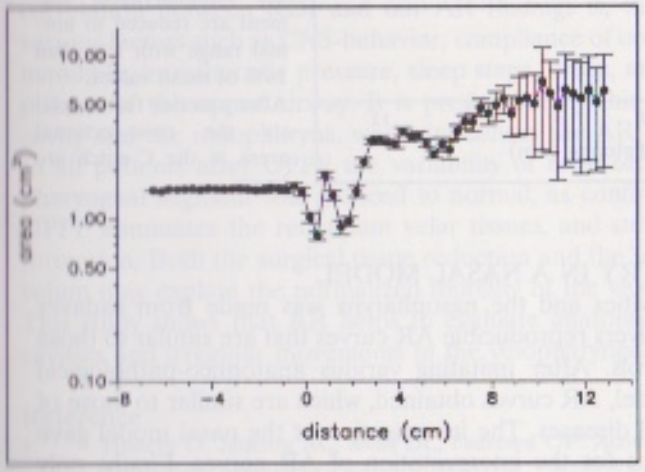

Fig. 2: Area distance function obtained by AR; mean curve and SD of 10 consecutive measurements within 3 s. Example (male, 52 years with turbinate hypertrophy, RDI=32) for patients with habitual snoring or OSAS: increased standard deviation of more than 31% of mean values in the velopharyngeal segment.

ACOUSTIC RHINOMETRY IN SNORING PATIENTS

The AR curves of snoring patients (Fig. 2) show some significant differences compared with normal controls. In patients with habitual snoring and OSAS we measured cross-sectional areas in the C-notch, that are significantly smaller than in normal controls, in the untreated as well as in the decongested state. This findings mean a nasal obstruction in the anterior third of the nose in 79% of cases with habitual snoring and OSAS as reported recently (4).

The intraindividual variability of cross-sectional areas in the velopharyngeal segment is significantly larger. 94% of all patients show values of standard devia-

tions larger than 31% (range 30-100 %) of mean values in this segment. The mean values of cross-sectional areas in the velopharyngeal segment are not statistically different between habitual snorers and patients with OSAS and/or normal controls. Furthermore the degree of SD and/or the mean values are independent of RDI. In 46 patients, 3 to 6 months after uvulopalatopharyngoplasty (UPPP), we measured a striking change in the intraindividual variability of the nasopharyngeal cross-sectional areas: we found the same degree of variability in all 46 patients after UPPP as in normal controls (fig. 3).
The mean values of cross-sectional areas in the nasopharyngeal segment before and after UPPP in the individual remain unchanged.

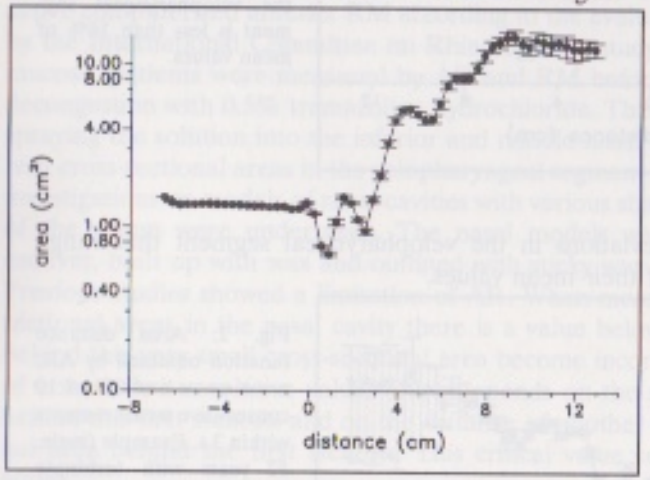

Fig. 3: Area distance function obtained by AR; mean curve and standard deviations of 10 consecutive measurements within 3 s.
Patient of fig.2 three months after UPPP and anterior turbinoplasty. SD in the velopharyngeal segment are reduced to normal range with less than 16% of mean values.
After anterior turbinoplasty the cross-sectional areas in the C-notch are larger.

ACOUSTIC RHINOMETRY IN A NASAL MODEL

A model of the nasal cavities and the nasopharynx was made from cadaver specimens. This model delivers reproducible AR curves that are similar to those obtained in normal controls. After imitating various anatomico-pathological conditions in the nasal model, AR curves obtained, which are similar to those of patients with defined nasal diseases. The investigation of the nasal model gave two important informations for the interpretation of AR curves. Firstly, only total occlusion in the choana resulted in AR curves with cross-sectional areas less than 0.1 cm^2. Secondly, occlusion in the velopharyngeal segment resulted in AR curves, which reflect the dimensions of both nasal cavities, because the acoustic signal is reflected in the nasopharynx and returns into both nasal cavities. Calculating the AR mean curve with SD in a series with increased velopharyngeal occlusion, we received similar patterns of curves as in our snoring patients.

DISCUSSION

Acoustic rhinometry is a quick, non-invasive and objective method to measure the cross-sectional areas and volumes of the nasal cavities. In the nasopharynx

AR computes cross-sectional areas that vary because of the dynamic variations of the soft palate. AR curves can only be interpreted in connection with the rhinoscopic and endoscopic findings of each individual. In a previous paper (5) we could show, that in 67% of patients with habitual snoring or OSAS a moderate or marked nasal obstruction in the anterior third (C-notch) is characteristic. Here we report on the analysis of the velopharyngeal segment by AR and endoscopy. Clinically recognizable irregular movements of the soft palate in rhonchopaths can be visualized by AR in 94% of all patients. Nonsnorers show a small intraindividual variability of the cross-sectional areas in the nasopharyngeal segment with SD not larger than 16 % of their mean values, whereas in chronic rhonchopaths the irregular movements of the soft palate are correlated with increased SD of cross-sectional areas in the velopharyngeal segment. We measured values of SD larger than 31% of mean values in all snoring patients. There was no correlation between of the degree of variability of cross-sectional areas in the velopharyngeal segment and RDI. The classification between patients with OSAS (RDI > 10) or habitual snoring (RDI ≤ 10) was not reflected by AR. Thus we think, that AR can be used as a screening test for two features of rhonchopaths, firstly the obstruction in the anterior third of the nose and secondly the velar hypermobility. The reason, that we could not find a correlation between RDI and our AR findings is, that RDI is influenced by various factors such as CNS-behavior, compliance of oropharynx, anatomy of the mandible, intrathoracic pressure, sleep stage, drugs, and among them the compliance of the upper airway. It is predominantly this compliance of the nasal cavity and the nasopharynx, which influences the AR findings.
In all patients after UPPP the variability of cross-sectional areas in the velopharyngeal segment was reduced to normal, as confirmed by videoendoscopy. UPPP eliminates the redundant velar tissues, and stabilizes the velum by scar formation. Both the surgical tissue reduction and the solid scar formation in the velum may explain the normalized mobility of the velopharyngeal sphincter.
This study shows that AR helps to evaluate anatomical stenoses of the nasal cavities and irregular movements in the velopharyngeal segment.

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Therapeutic Performance of Nasal and Paranasal Operations in Recent Years

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INTRODUCTION

In recent years, nasal operations in Japan have increasingly tended towards conservative nasal surgery instead of conventional radical operations based on Caldwell-Luc's method. This trend is due to a reduction in the incidence of the major disease of chronic sinusitis, milder pathology of chronic sinusitis patients, coupled with worldwide advances in medical optical equipment. We will report here on a survey of nasal surgery, primarily conservative fiberscopic endonasal sinusectomy (1) (2), performed over the past ten years, and discuss the therapeutic results of these operations.

METHOD

A total of 3,460 operations have been performed at our hospital over the past ten years, of which nasal operations account for 2,408 giving an annual average of 240 operations.
In order to investigate postoperative therapeutic performance, we selected 1,043 nasal surgery patients who were asked to fill out a questionnaire, 555 questionnaires were returned completed. The sex and age range of the sample are shown in Fig. 1.

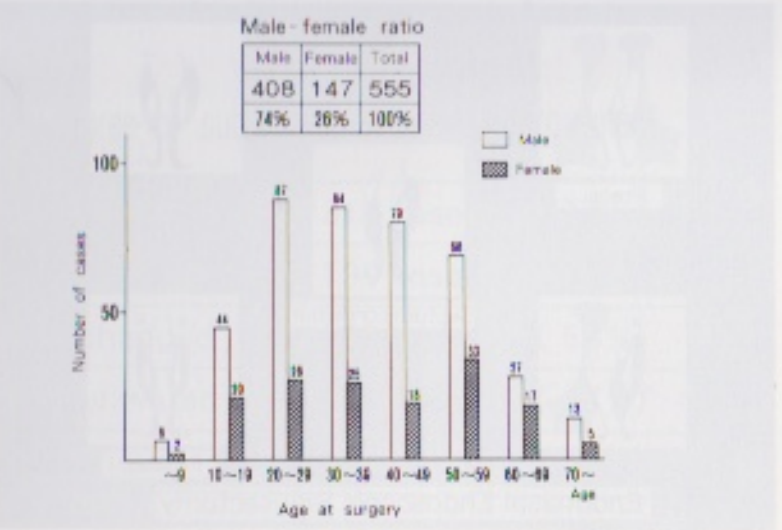

Fig. 1: The sex and age of 555 questionnaires

Nasal disorders included deviation of the nasal septum, chronic sinusitis, recurrent sinusitis, allergic rhinitis, postoperative maxillar cyst, sinusitis in children and dental sinusitis.
These patients all underwent conservative nasal surgery using the Takahashi's Method (3) (4). The fundamental concept on which this treatment is based is that abnormalities in the shape of the nasal cavity play a major role in paranasal sinus disorders. The actual surgical methods, as indicated in Fig. 2, were not uniform for deviation of the nasal septum and other abnormalities in the shape of the nasal cavity, and disorders in the shape of both paranasal sinuses. Rather, the nasal cavity and paranasal sinuses were observed as a whole, and integrated and comprehensive surgery was performed combining correction of deviations of the nasal septum, turbinectomy and opening of each paranasal sinuses. A subsequent peroral operation was only performed when the pathology had progressed. Peroral surgery, i.e. radical surgery methods, however, have been avoided wherever possible in view of the problem of postoperative maxillar cysts. Moreover, we have utilized endonasal surgery for cyst opening of postoperative maxillar cysts as well.

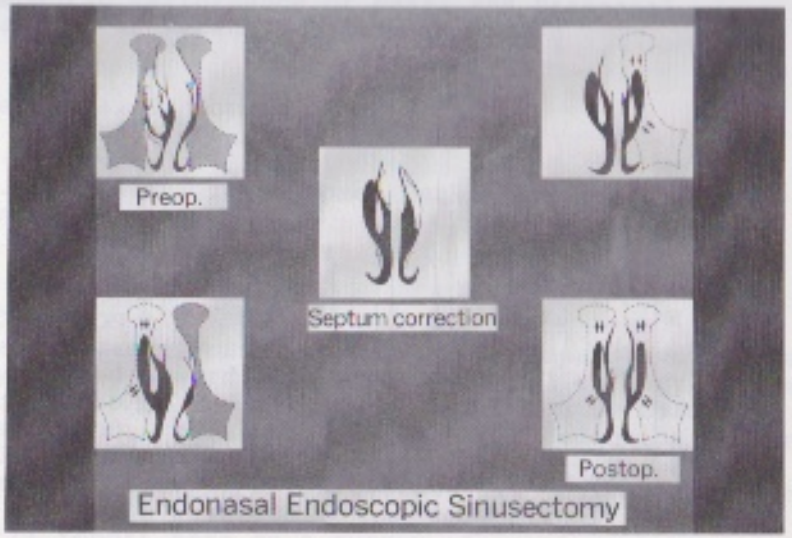

Fig. 2: Takahashi's Method

The operations that we have conducted can be classified by the surgery methods. The most common surgery, at 57.7% of the total operations, was surgery consisting of a conservative endonasal operation combined with correction of nasal septum deviations. Conservative endonasal operations combined with peroral surgery only account for 12.2% of total operations. This indicates that the number of patients with advanced symptoms are few in number and, at the same time, proves the therapeutic efficacy of conservative endonasal surgery.

THERAPEUTIC PERFORMANCE

1. Improvement in subjective symptoms

We analyzed the degree of improvement in the subjective symptoms reported by 555 patients after their operations by classifying them into four categories: cured, improved, unchanged and aggravated. As indicated in Table, the percentage of patients who answered that their symptoms were cured or improved came to 57.3% and 34.2%, respectively, giving a total of 91.2% of respondents indicating satisfaction with their treatment. The remaining 6.1% said that their symptoms were unchanged or aggravated, thus indicating dissatisfaction with their operative treatment.

Table 1. Degree of subjective symptom improvement

Degree of subjective symptom improvement

Cured	318 cases	(57.3%)
Improved	190 cases	(34.2%)
Unchanged	30 cases	(5.4%)
Aggravated	4 cases	(0.7%)
Unknown	13 cases	(2.3%)

(555cases)

2. Postoperative relief of symptoms

1,150 answers were analyzed in terms of postoperative relief of symptoms. This number includes patients who indicated multiple symptoms. Relief of nasal obstruction, one of the most common symptoms of nasal disorders, is top at 30.0% followed by those of head heaviness, rhinorrhea, and post nasal drip.

Next, we investigated the relationship between relief of symptoms and the degree of subjective symptom improvement. No patient answered that nasal obstruction had been aggravated in the degree of subjective symptom, as 72% answered cured, and 26% answered improved. In total 98% indicated that they were satisfied with the relief of nasal obstruction.

90% of patients responded that head heaviness, rhinorrhea, post nasal drip, olfactory disorder and headache had been cured or improved. Relief or cure of the above symptoms is regarded as an extremely important object of nasal surgery.

SUMMARY

In this survey of the postoperative therapeutic performance of 555 cases of nasal surgery, particularly conservative fiberscopic endonasal sinusectomy, it was found that conservative nasal operations accounted for 87.8% of the entire sample population and the therapeutic effects, (in terms of subjective symptoms) were found to be favorable in 91.5% of cases. These results suggest that conservative nasal operations will become the dominant form of nasal surgery in the future.

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MIGRAINES AND THE SINUSES, REPORT ON 441 CASES.

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INTRODUCTION

This report involves 441 patients(pts.) suffering from Headaches and Migraines. Diagnosis was directed to the rhinologic triggers that would alter the physiological functioning of the paranasal sinuses and the nasal airway; and hence initiate the pain stimuli. Treatment consisted in controling the allergy and infection as well as stimulants in the environment, hunger and stress. When the headaches were not releived completely this was followed by surgical correction of deformites of the nasal septum and para nasal sinuses.
It was found that all the pts. complained of other allergic symptoms (acephalgic migraine). These symptoms were recurent just like the migraines; they were abolished with the same treatment. In the management of this group of patients it was observed that intermitant allergic reactions whether central or periferal, immediate or delayed initiate pain stimuli in the nose and para nasal sinuses and lead to headache and migraine attacks. Successful diagnosis, treatment and prevention is presented.

PATIENTS AND METHODS.

Four hundred and seventy seven consecutive pts. were seen. Thirty six dropped out before any diagnosis was carried out; 441 pts. completed the diagnosis.
These are highly motivated individuals who have seen a minimum of 5 Doctors of various disciplines; and have tried various treatments. They are told before they come that we diagnose the causes of the headaches and do not give narcotics, analgesics,cafergot or any other medicine that treats the symptoms. No workman compansation cases are accepted, nor cases of traumatic headaches that may benefit in any way by not recovering.

DIAGNOSIS:

Complete histories & Physicals were done and all usual organic causes are ruled out.
1. The location of the headaches are carefully drawn on figures of the head and neck. 2. The frequency and severity of the headaches in the last 6 months are documented. 3. Associted intermitant symptoms are noted e.g.dizzyness, fullness of the ears, hearing loss, nasal and post nasal drip, itchyness, blurring of vision,

tightness of the chest, variant angina, indigestion, heartburn, mouth ulcers, fatigue, excessive sleep, depression,unfocused feeling and anxiety. 4. Cultures of nasal secretions are taken; when the maxillary or frontal sinuses are tender. 5. Rhinoscopy is done and deformities of the nasal septa and mucosal impaction with the turbinates are documented. 6. Allergy work is done next. A combination of the intradermal skin test, the RAST test(Wide et al,1972) and the 4 day diversified rotating diet are used. They are screened for inhalents (seasonal pollens, molds, house dust mite and chemicals). Also the most frequently eaten foods are tested; and the offending foods are identified. 7. A brief social history is taken and the severely stressed individuals are known.

TREATMENT

1. All patient are started on mucolytics (iodinated glycerol or guaifenesin). 2. Antibiotics are given whenever the maxillary or frontal sinuses are tender. 3. Diversified 4 day rotating diets are followed excluding the offending foods. 4. All patients have to enter in their diaries exposures, foods, headaches other symptoms etc. 5. Severely stressed individuals are made aware of avenues to resolve their conflicts. 6. When patients continued to have headaches after the first 2 weeks, C.T.scans of the para nasal sinuses are done, and when these were found to be abnormal, surgical treatment follows.

Abnormalities that would indicate surgery are:

a. Deformed nasal septa producing mucosal contact and obstructing the para nasal sinus ostia and one or both nostrils. b. Deformed, enlarged or pneumatised middle turbinates. c. Disease in either anterior ethmoids. d. Diseased frontal recess in individuals complaining of headache in the forhead extending upwards. e. Disease in the maxillary sinuses in patients complaining of pain in the suboccipital region and extending down the neck.

Application of cocaine 10% in the the diseased area of the nasal mucosa abolishes the pain or may reduce its severity. It convinces the patient of the site of their headaches.

During surgery our aim would be, to eliminate mucosal impaction in the nose,eliminate disease in the sinuses to leave them with good drainage possibilities; establish a good nasal airway that will permit the patient to sleep on both sides.

If some pain persists after surgery; repeat the C.T. scan and deal with what abnormality it showed. Also repeat cultures of the nasal secretions and treat accordingly.

Usefull hints on surgery for headaches:

1. To prevent adhesions post operatively between the lateral surface of the middle turbinate, and the medial surface of the inferior turbinate when anterior ethmoidectomy is performed; it was found necessary to cut at least 1 cm. of the anterior tip of the middle turbinate.
2. In patients with frontal headaches; open the ethmoid infundibulum, perform partial middle turbinectomies and explore the naso-frontal duct lateral to the superior anterior ethmoid cells.
3. Exploration and widening of the sphenoid ostia are necessary in patients with headache on the top of the head.
4. Post rhinoplasty headache pts. might need partial middle &/or inferior turbinectomies as well as out fraturing of the nasal bones.
5. When the C.T.scan shows a lateraly curved medial wall of the maxillary sinus, creating a very narrow tunnel to the normal ostium; in a pt. with suboccipital pain; a good size antrostomy is created in the inferior meatus.
6. The firm swellings that are often found on each side of the nasal septum can be flattend by performing deep burns with the cautery needle and then injecting 2 drops of Depo Medrol 40 mg.to the cc. In this manner mucosal contact is treated.

Post operatively all the patients are reminded daily for the first 2 weeks to follow their 4 day diversified diet and to continue eliminating their offending foods.

RESULTS

No.of pts. seen		477
No. of pts.treated	441	
Pts.free of headache	439	
Pts + intermitent headache	1	
Pts + contineous headache	1	

Table 1.

Total No. of pts.that had dev.nasal septa		225
Pts. treated for allergy & infection		225
Pts. that had to have surgery	89	
Pts with dev.nasal septa that had no surgery		136

All the relapses that were recorded by the pts. in their diaries are shown. Some pts. reacted to multipl stimuli Relapses caused by food and drinks were the highest.

Table 2.

Analysis of relapses in all pts. treated.

Dietary	328
Infection	120
Environmental	37
Stress	10

Nasal secretions of pts. that had tender maxillary &/or frontal sinuses were cultured, and are showen in table3

Table 3

Cultures of nasal secretions of 86 headache pts.

Staph.aureus Coag.+ve	43
Normal flora	28
Diphteroids	6
E.Coli	3
Entero Bact.Cloaca	3
Haemophilus influenza	2
Proteus Mirabelis	2
Pseudomonas Aeruginosa	1
Klebsiella Pneumoniae	1

One might ask the question whether cultures of the nasal secretions may give a clue if the patients will need surgery for control of their headaches. Looking at the pts.(with dev.nasal septa) that cultured staph. coagulase +ve out of 28 only 18 needed surgery (64%). The remainder were treated medically. Those similar pts. that cultured normal flora; 14 out of 16 needed surgery(88%). Hence the intial culture does not seem to carry much prognostic value.

The two patients that continued to have headaches, have stopped coming for follow up; they both admit though that the severity of the headache was reduced down by 50%.

DISCUSSION

It is thought that intermitant central release of histamine & serotonin (Herberg 1973) in an allergic patient will alter the balance of noradrenaline and serotonin in the hypothalamus, and hence produce changes in the central autonomic control (Wilson et al 1980;Hoover 1987). These reactions affect cell membrane permeability at the target organs by interferance with Calcium transport across the membranes (Tasaka et al 1986). Mucus membranes of the nose, para nasal ostia and linings become aedematous from the fluid retension. Similar effects can be taking place in auditory patways, inner or middle ears producing the vertigo & hearing loss.
Interferance with cell membrane permeability in smooth muscle cells will lead to their shortening as in asthma & can lead to intermitant spasms of vessels leading to

T.I.As, variant angina etc.; and also to increase in the bulk of turbinates due to reactive dilatation that follows the initial spasm as in Reynaulds disease. This will produce impaction & mucosal contact, and close the paranasal ostia. Various kinds of headaches will result depending on the location of the stimuli of the nasal mucosa(McAuliffe 1943; Holmes 1950). The headaches in the suboccipital region is produced by convergence of C1,2 & 3 into the neurons of the 5th nerve (Kerr 1961 List 1968).
Treatment with mucolytics control of the bacterial infection seem to decrease the severity of the pain but not the frequency.Local vasomotor changes in the erectile tissue of the turbinates is produced by stress such as exhaustion, anxiety, sexual excitement(Fenton 1941).Also extreems of weather and hunger. Thus mucosal contact and painful stimuli are initiated. This effect is increased in the presence of infection(McAuliffe et al 1943).

CONCLUSION

The management of 441 patients with severe Headaches & Migraines is presented. Diagnosis of the rhinologic triggers and their treatment is expained. The excellent outcome of the combination of medical & surgical treatment of the infection, allergy & pathalogical deformities & disease of the paranasal sinuses and nasal septum lead us to conclude that Headaches and Migraines of any type are completely treatable and preventable.

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Complications of the Maxillary Sinus Irrigation Caused by Misdirected Tip of the Trocar

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INTRODUCTION

Since it was first introduced by Dr. Mikulicz in 1887 and then by Dr. Schmidt in 1888, antral irrigation has been commonly employed by ENT doctors as one of the modalities for the diagnosis and treatment of maxillary sinusitis. Though a relatively simple and easy method, antral puncture and irrigation still has some risks of complications such as local bleeding, infection, air embolism, anaphylactic shock, misdirected position of the trocar tip and so on. There are several routes of entry into the maxillary sinus in making punctures, but through the inferior meatus of the nose is the route most popularly used by the ENT doctors in clinical practice. This presentation mainly focuses on the complications caused by the misdirected position of the trocar in making antral irrigations through the inferior meatus of the nose. Through the schematic illustrations we can understand the mechanisms of these accidents. Thus we may avoid the untoward complications as less and as minimal as possible.

MATERIALS AND METHODS

Antral punctures via the inferior meatus were performed to 327 cases in Taipei Medical College Hospital from 1986 through 1990. Detailed history were obtained and physical examinations were done. Roentgen examinations including Waters', Caldwell and lateral views were done and all showed cloudiness of the maxillary sinuses. Antral punctures with irrigation or instillation of contrast media were done for either diagnostic and/or therapeutic purposes through the inferior meatus under local anesthesia. Complications caused by misdirected tip of the trocar while making punctures were classified into three categories by the author as follow :

I. Intra-antral
   (a) Submucoperiosteal
II. Extra-antral
   (a) Intra-orbit
   (b) Subperiosteal space of the cheek soft tissues
   (c) Pterygopalatine fossa
   (d) Inferior meatal-submucoperiosteal space
III. Combined types

RESULTS

Among the 327 cases undertaken antral punctures, 177(54%) were male and 150(46%) were female. Age distribution was from 3 to 65 years old and peak age was 13 to 20 years old (31%). Unilateral sinusitis was seen in 192 cases(59%) while bilateral in 135 cases(41%). Total number of punctures were 462. Total number of complications caused by misdirected tip of the trocar were 19(4.1%).(Table.1)

Table 1. Incidence of Complications Caused by Misdirected Tip of the Trocar While Doing Antral Puncture

Complications	Case No.	%
I. Intra-antral		
(a) Submucoperiosteal	8	1.73
II. Extra-antral		
(a) Intra-orbit	0	0
(b) Subperiosteal space of the cheek soft tissues	2	0.43
(c) Pterygopalatine fossa	0	0
(d) Inferior meatal-submucoperiosteal space	6	1.30
III. Combined types		
I(a)+II(b)	1	0.22
I(a)+II(d)	2	0.43
Total	19	4.11

DISCUSSION

There are several routes of entry into the maxillary sinus in making punctures,(Fig.1) :
(a) through the antral ostium
(b) through the membranous part of the middle meatus
(c) through the inferior meatus and
(d) through the canine fossa.
The third one (c) through the inferior meatus of the nose is the route most popularly used by the ENT doctors in clinical practice. Anatomically the maxillary sinus is three-dimensionally surrounded superiorly by the orbit, anterolaterally by the cheek soft tissues, medially by the nasoantral wall with attached structures , posteriorly by the pterygopalatine fossa, and inferiorly by the palate. The inferior barrier, palate, is made of hard bony structure not easy to get damaged by the needle puncture. Correct position of the puncture needle is shown on the left side of Fig.2, and there will be smooth irrigation flow from the syringe through the inferior meatus, antral cavity, natural ostium, then into the nasal cavity. Any abnormal contents, mucus secretion (purulent or nonpurulent), blood clots, inflammatory products can be collected for bacterio-logical and cytological studies. On the right side of

Fig.2 shows two possibilities, if the tip is entirely placed in the submucoperiosteal space of the antral mucosa, it will induce separation and dissection of the space due to forced irrigation. Local pain and bleeding will occur. As we know the tip of the needle is usually oblique, so it has the chance to override partly in the antral cavity and partly in the submucoperiosteal space of the antrum. On this occasion, there might be some antral contents washed out through the natural ostium into the nasal cavity at the start, but dissection and separation proceed in the meanwhile, and direct towards the antral ostium, make strangulation and constriction from outside, finally impede the antral irrigation flow greatly. Fig.3 shows the extra-antral intraorbital complication. The tip is in the orbit. This is the so called through-and-through penetration and is one of the most dangerous complications. Eyelid edema, local pain, double vision, infection, and even loss of vision may ensue. Fig.4 shows misdirected tip in the Extra-antral subperiosteal space of the cheek soft tissues. This is the complication most commonly seen in the antral puncture practice. Cheek swelling develops, and local pain is complained of, too. Fig.5 shows trocar tip in the pterygopalatine fossa. Local massive bleeding and pain are the chief clinical manifestations, because there are many vessels in this space. Fig.6 shows misdirected tip in the inferior meatal submucoperiosteal space. The inferior meatus is blocked due to submucoperiosteal bulging and this swelling may extend medially to the nasal floor and the base of the nasal septum on the same side and posteriorly to the soft palate of the nasal aspect. Fig.7 shows combined type complications. These are the combined forms of the above-mentioned if the sites are adjacent, as partly in the inferior meatus and in the antral cavity, partly in the antral cavity and in the orbit, or partly in the subperiosteal space of the cheek soft tissues, etc.

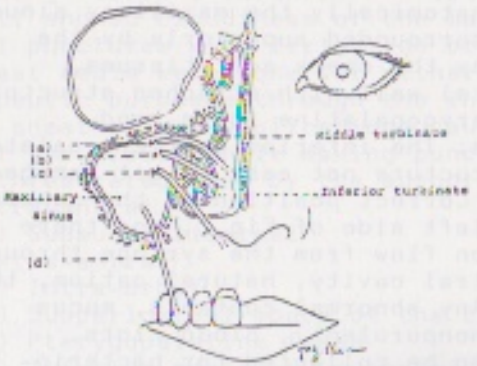

Fig. 1
Routes of Entry

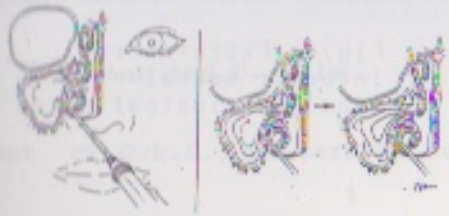

Fig.2
Normal Antral Irrigation(L't)
Abnormal Antral Irrigation(R't)

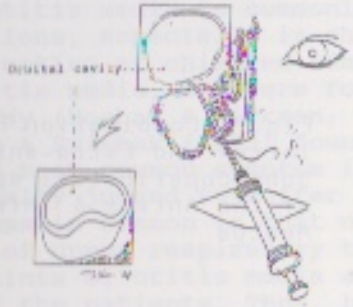

Fig.3
Extra-antral Intraorbital Space

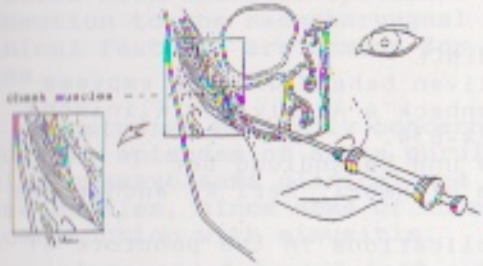

Fig.4
Extra-antral Subperiosteal Space of the Cheek Soft Tissues

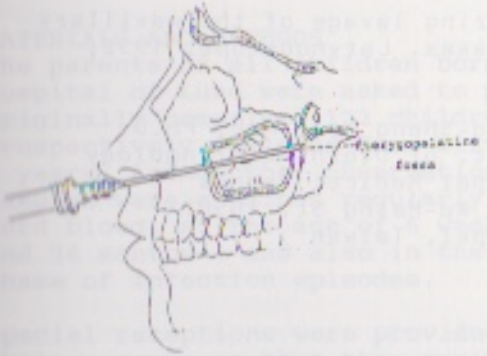

Fig.5
Extra-antral Pterygopalatine Fossa

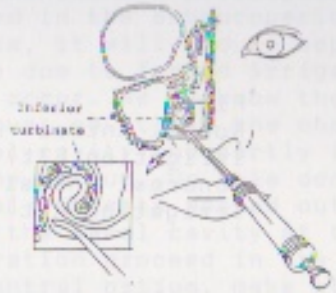

Fig.6, Extra-antral Inferior meatal-submucoperiosteal space

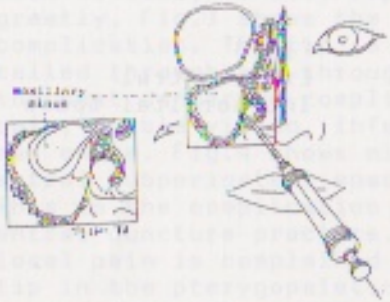

Fig.7, Combination Form Intra- and Extra-antral Submucoperiosteal spaces of the Antrum & Inferior Meatus

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INTRODUCTION

That otitis media is commonly associated with sinus infections, especially in children, is well-known. Thus, when looking at children admitted for tube insertion due to otitis media, 62% were found to have opaque sinuses at X-ray (Hoshaw & Nickman, 1974). The other way round, Kogutt & Swishuk (1973) found otitis media to be the second most common symptom in children who were clinically judged to suffer from sinusitis. Other symptoms in common is that nasal discharge and other signs of upper respiratory tract infections precede the complaints of otitis media and sinusitis in more than 90% of the patients. Thus, besides from the anatomic similarities between the middle ear and the sinus - cavities with ciliated epithelia and a rather narrow connection to the nasopharyngeal region - several clinical features are common for infections at these sites.

Our own studies basically concern children with recurrent episodes of acute purulent otitis media and I will present some clinical and immunological data from these studies, since some of them might also be relevant in conjunction with sinusitis.

First we would like to give a short presentation of the design of one of our studies to which we will refer rather frequently.

MATERIALS AND METHODS

The parents of all children born at the University Hospital of Lund were asked to participate. The study originally comprised 122 children. They were prospectively followed from birth until the age of 3 years. Among other observations on this group, blood samples were obtained regularly from the children - from cord blood, at the age of 6 weeks, 3, 6, 12, 18, 24, 30 and 36 months - and also in the acute and convalescent phase of infection episodes.

Special receptions were provided for the children and their parents so that they could easily reach one of the investigators.

At the end of the study there were 113 children left. Among these, 13 children turned out to have suffered from recurrent AOM - defined as 6 or more episodes of AOM during one 12-month period - and 29 children turned out to have been "extremely healthy" and without any AOM episode.

RESULTS AND DISCUSSION

One factor said to be important for the occurrence of respiratory tract infection (RTI) and AOM is the way the children are cared for during day-time. We found the frequencies of both RTI and AOM to be significantly higher during the second year of life in children attending day-care centers (Harsten et al., 1990).

The findings of more episodes in children cared for at day-care centres are in full agreement with many other studies. However, I do not believe that the day-care centres are responsible for the fact that certain children are so much more otitis-prone than others.

In our study the total number of AOM episodes were 300 (Harsten et al., 1990). The AOM episodes in the 13 rAOM children is illustrated in Fig 1. When comparing these children with the other 100 children, no differences were found in distribution of sexes, familial allergic predisposition, number of family members or living conditions. However, 10/13 (77%) of the children with

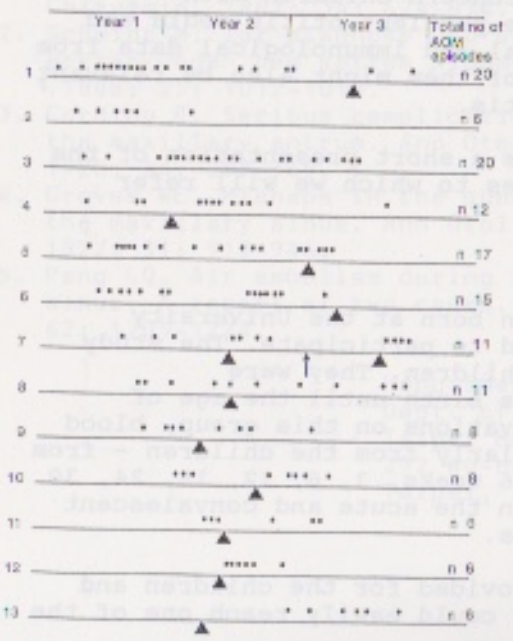

Fig. 1. AOM episodes (●) as related to enrolment in day care centre (▲) in 13 children with recurrent AOM. † denotes returning to home care.

rAOM had a family history of recurrent episodes of AOM as compared to 9/29 (31%) of the "extremely healthy" children (Harsten et al., 1989).

When looking at the pattern of AOM episodes in relation to form of day care in the 13 rAOM children it also seems obvious that factors within the child are of importance for the development of recurrent infections (Fig. 1).

Among other things the host defence against the bacteria most commonly associated with otitis media as well as sinusitis might vary from one individual to another. Pneumococci and *Haemophilus influenzae* are the most common pathogens in acute otitis media. A coordination of humoral factors - antibodies and complement -, resulting in opsonization, is a prerequisite for efficient phagocytosis of pneumococcal bacteria. The final result of the reactivity between antibodies and complement on the surface of Gram-negative bacteria, like *H.influenzae*, usually is the lysis of the bacteria although enhanced phagocytosis is seen as well.

Thus, the presence of antibodies is important and a relationship between low serum concentrations of antibodies against some pneumococci and of bactericidal antibodies against *H.influenzae* has been indicated in otitis-proneness.

When comparing the concentrations of IgG antibodies against pneumococcus type 6A, which is one of the most common types in AOM, in 2-year-old children already suffering from recurrent AOM to age-matched healthy controls, it was concluded that the children with recurrent AOM as a group had lower antibody levels than the controls (Prellner et al., 1984) - a statement that has also been verified by others (Freijd et al., 1984).

However, the results also strongly indicated that the group with recurrent AOM was heterogeneous in this respect - one subgroup with very low antibody levels and one with levels on par with the controls. Measurements of antibodies against other pneumococcal types associated with recurrent AOM have also been performed, and they show similar differences. But in all studies the differences have been most pronounced with regard to pneumococcus type 6A (Prellner et al., 1984).

Though a problem while the child is suffering from the disease, clinical data show that recurrent episodes of AOM cease with increasing age of the child. That this is parallelled with an increase in pneumococcal antibodies is demonstrated in Fig. 2, which shows the antibody levels 6 years later in the same children studied at the

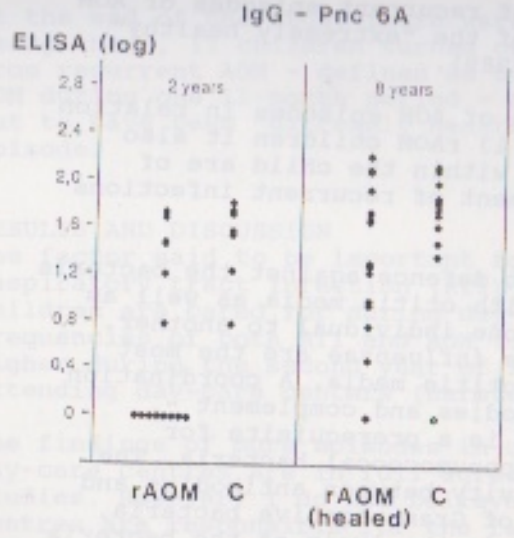

Fig. 2. Specific IgG antibody concentrations (logarithmic values) to pneumococcus type 6A in serum in children, at 2 and 8 years of life, who during infancy suffered from recurrent AOM (rAOM) and in healthy controls (c). Values on the zero line denote original untransformed values = 0.

age of two (Fig. 2). The differences were still to be seen though less pronounced. In adulthood the differences had disappeared (Prellner et al., 1984).

When studying the antibody levels followed from birth it was found that the concentrations of antibodies against pneumococcus type 6A were consistently lower in the children with recurrent AOM than in the healthy children. This finding was obvious already before the development of any AOM episode (Prellner et al., 1989). Concerning the low levels of pneumococcal antibodies, this was seen within the IgG and sometimes IgA classes but never for IgM antibodies.

The data from these various investigations might indicate a delayed switch-over from IgM to IgG and IgA antibody production against pneumococcal types associated with AOM. The hypothesis of immunological immaturity in children with recurrent AOM derives further support from the report by Pelton and coworkers (1988) of lower antibody response to pneumococcal vaccination in young children with recurrent AOM.

In children designed as otitis-prone, the findings of lower antibody concentrations also before development of the disease, as well as the higher frequency of histories of otitis-proneness in their families, strongly support the involvement of hereditary factors in otitis-prone children.

In a newly performed study concerning genetically determined factors - human leukocyte antigens (HLA) - a correlation to development of recurrent acute otitis media was indicated. Thus, the frequency of HLA-A2 was significantly higher and that of HLA-A3 significantly lower in children with recurrent AOM than in controls (Kalm et al., 1991).

So far, these same factors have not been investigated in patients with prolonged or repeated sinusitis. However, the possible influence of the immune status in these patients is supported by the recently reported findings by Scadding and coworkers (1990), of lower subclass levels for IgG3 in patients with chronic or recurrent rhinosinusitis.

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Computed Tomography: Anatomical Aspect

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MATERIALS AND METHODS

Computed tomograms obtained from 106 patients in the years 1985-90 were reviewed. The great majority were suffering from sinusitis or nasal polyposis. Six of them were normal subjects, used in a previous research (13); twelve were tumours. Each case was studied by means of axial scans, 1 mm in width, parallel to the floor of the anterior cranial fossa. Whenever possible, axial scans were complemented by direct coronal scans.

A questionnaire including 12 items was developed and delivered to 5 observers who examined independently the radiograms. Among the available responses, there was always the one "not assessable", to be applied with a rather strict criterion: e.g., in some patients the absence of the appropriate coronal or axial section, or of both of them, could elicit unreliable answers if only a "yes/no" choice was given.

Each item of the questionnaire is reported here, with a short comment about its significance. The percentages given are the average of those obtained by each observer; to prove the homogeneity of judgements, which was generally very good, the minimum and maximum are also indicated. The data obtained from our investigation are compared with those drawn from anatomical studies of the literature.

1. SUPRAORBITAL RECESS.

Behind the posterior wall of the frontal sinus, some ethmoid cells may invade the ceiling of the orbit. These cavities have been named supraorbital recess, or supernumerary frontal sinus, or frontoorbital cells. They should not be mistaken for the so-called frontal bullae, which are ethmoid cells creeping into the frontal sinus floor. In the neurosurgical approach to the orbit, performed from the anterior cranial fossa, the presence of this recess may jeopardize the sterility of the operation field. In case of inflammatory pathology, its safe opening demands an external (transorbital) ethmoidectomy, as even the thinnest telescope cannot adequately expose it.

In our material, a supraorbital recess was found in 18,98% (min. 11%; max. 25%). In anatomical literature the percentages range from 10% (11) to 21% (4). In Japanese skulls the number was by far

greater: 61% (10).

2. DEHISCENCES IN THE LAMINA PAPYRACEA

Defects in this very thin plate are common. Besides those produced by earlier or current diseases, some are assumed to be spontaneous, due either to incomplete ossification or to an excessive pneumatization. A dehiscence in the lamina papyracea demands caution during exenteration of the most lateral ethmoid cells, in order to avoid injuries to the superior oblique and rectus medialis muscles, which are quite close to the orbital plate. Moreover, when a gap exists, bleeding at the end of surgery may cause a postoperative orbital hematoma.

In our material, dehiscences were judged to be present in 32%; among them, 23,40% were in the anterior ethmoid, 6,73% in the posterior and 2,40% in both of them. These percentages are at variance with anatomical investigations, which reported much lower numbers, ranging from 5,6% (6) to 13,5% (12). It is therefore presumable that our observers considered as actual gaps simple rarefactions of the bony plate. However, it must be remembered that from a surgical standpoint it makes no difference whether a partition is extremely thin or actually defective, as in both cases the vulnerability of the underlying structures is practically the same.

3. PNEUMATIZED MIDDLE TURBINATE

An air cavity within the lamina recurvata (i.e., the middle turbinate free hanging portion), named by Zuckerkandl (15) "concha bullosa", may impinge upon the wall of the middle meatus, affecting sinal drainage and ventilation. Moreover, the cell itself may become infected. Therefore, it must be identified on CT scans in order that its treatment may be incorporated in the surgical plan.

A pneumatized middle turbinate was imaged in our material in 21,38%. In 7,25% the cavity was on the right side (min. 5,36%; max. 8,86%), in 7,85% on the left (min. 6,45%; max. 9,09%) and in 6,28% on both sides (min. 3,80%; max. 8,82%). The only percentage found in anatomical literature is 8% (8), but a surgeon reported in his patients higher values (17%) (1).

4. PRESENCE OF A SPHENOMAXILLARY PLATE

In cases of remarkable pneumatization not only the ethmoid, but also the sphenoid may abut on maxillary sinus. The partition between them takes the name of sphenomaxillary plate and lies next to the ethmomaxillary plate. Its identification is crucial in transantral ethmoidectomy, to avoid mistaking the sphenoid sinus for posterior ethmoid cells.

In our material, a sphenomaxillary plate was observed in 14,67%

(min. 11,62; max. 18,06%), while the only percentage available from anatomical studies reports 18% (15).

5. HALLER'S CELL

The middle turbinate basal lamella merges with the ethmomaxillary plate at its most lateral end. Here it may be hollowed out by one or, less frequently, more cells, located between maxillary sinus and orbit, the so-called Haller's cells. Owing to their lateral situation, they may be disregarded during intranasal ethmoidectomy. A Haller's cell was observed in our material in 10,04% (min. 6,55%; max. 12,60%). In the few anatomical studies which assessed its presence, it ranges from 4% (3) to 11% (14).

6. ONODI'S CELLS

They are posterior ethmoid cells encroaching the upper portion of the sphenoid sinus; therefore, they are located between the sinus and the floor of the cranial fossa. Their importance lies in their relationships with the optic nerve, because, when they are present, the nerve runs invariably along their lateral wall.
In anatomical studies they were encountered in a percentage round 12% (9,15). We obtained an average incidence of 13,94%, with a minimum of 9,09% and a maximum of 18,90%.

7. OPTIC NERVE

The optic nerve abuts on either the sphenoid sinus, or on posterior ethmoid cells, or on both of them. The thickness of the bony wall separating the nerve from the cavity is less than 1 mm on the average (8). Partitions of such thinnes can obviously be interpreted as defective on CT scans. Actually, dehiscences along the optic nerve were observed overall in 9,66% of our cases; among them, 8,22% (min. 7,58%; max. 9,55%) were at the level of the sphenoid sinus. In anatomical literature, true gaps are reported in about 4% (2,9).

8. INTERNAL CAROTID ARTERY

The bony layer dividing the artery from the sphenoid sinus is usually very thin and dehiscences were reported in 8% (2). In our material, the total of dehiscences was 5,87% (min. 2,58%; max. 9,52%), of which 1,09% were bilateral.

9. MAXILLARY NERVE

In more than 1/3 of cases, the maxillary nerve produces a remarkable bulge on the inferior part of sphenoid sinus medial wall. True dehiscences were observed on specimens in 2% (2), while in our material they were estimated to be present on average in 4,61% of cases (min. 1,81%; max. 6,77%).

10. VIDIAN NERVE

The average percentage of vidian nerve dehiscences was in our material 10,74% (min. 2,81; max. 14,55%), in good agreement with the only anatomical study which reports 10% (8).

11. LEVEL DIFFERENCE BETWEEN CRIBRIFORM PLATE AND ETHMOID ROOF

The cribriform plate, corresponding to the vault of the nasal fossa is generally at a lower level than the ethmoid roof. The interstice beween them forms the olfactory pit, where the olfactory bulbe is lodged. The deeper the pit, the wider the relationships between upper ethmoidal cells and endocranium, because not only the roofs, but also the medial walls of the forner come into contact with the latter. Therefore, previous knowledge of the situation is fundamental, especially in case of endoscopic surgery where stereoscopic view and hence direct appreciation of the distance is lacking.
The difference in height between cribriform plate and ethmoid roof ranges between 4 and 7 mm in 70% of cases (5). According to Lang (8), the average is 5,03 mm, with a minimun of 0 mm and a maximum of 15,6. The overall average between our observers was 5,94 mm; the lowest measure was 1,3 mm and the highest 17 mm.

12. DEPTH OF THE SPHENOETHMOIDAL RECESS

The sphenoethmoidal recess is best imaged on axial scans, where it appears as a more or less pronounced lateral bending of the nasal cleft. It is important both from a pathological and surgical standpoint, as secretions from posterior cavities tend to collect here and because it must be traversed to gain access to sphenoid sinus. In our material, the recess depth, measured from the most posterior edge of the nasal septum, was 4,34 mm; the minimum recorded was 1,30 mm, the maximum 12 mm. These figures correspond well with those of Lang (7), who reported an average of 4,3 mm, with a minimum of 1,5 mm and a maximum of 12 mm.

CONCLUSIONS

There is close agreement between data obtained from the scrutiny of CT scans and those provided by anatomical dissections. Some discrepancies only occurred when the judgment concerned the integrity of a thin bony plate, as might be expected, because the CT resolution power is not unlimited. On the whole, results thoroughly validate the use of CT for studying anatomical variations in the area of paranasal sinuses.

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Computed Tomography in Rhinology

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Basically there are four imaging modalities used for the evaluation for the nose and paranasal sinuses:
- ultrasound
- plain x-ray (Waters view, Caldwell view, underexposed basal view)
- computed tomography (CT)
- magnetic resonance (MR).

Conventional tomography has been superseded completely by CT. While ultrasound and plain x-ray are sufficient methods in a variety of pathological conditions in the nose and paranasal sinuses, we still have to consider a lot of different diseases in this area, which require further diagnostic management by modern imaging techniques. In the present paper the diagnostic value of CT in rhinologic diseases will be presented.
According to the suggestions of Som (1985), axial scans should be performed first. Depending on the site of interest (i.e. palate, orbital floor and roof, ethmoid and sphenoid roof) additional coronal scans might be necessary. The slice thickness should be no greater than 4 mm in routine examinations. The CT examinations should cover all paranasal sinuses, thus beginning at the maxillary alveolus and ending above the frontal sinuses (Som 1985). Contrast media should be applied whenever possible in order to differentiate between inflammatory and tumorous tissue.
We distinguish four major groups of abnormal conditions in the nose and paranasal sinuses:
1. Congenital variations and anomalities
2. Inflammations
3. Trauma
4. Neoplastic lesions

1. Congenital variations and anomalities:
An extensive discussion of congenital variations is beyond the scope of this article; it must be remembered, however, that there is a great variability in sinus development and pneumatization. Sometimes, sinuses may even be absent. As a life-threatening deformity, choanal atresia must be taken into consideration as a cause of respiratory distress shortly after birth. Eventhough the diagnosis is usually set by clinical examination, CT evaluation might be helpful to distinguish between osseous or fibrous obstruction of the choanae. Congenital encephalocele is another abnormality which has to be regarded in the differential diagnosis of nasal polyps in young children. The imaging method of choice, however, in intranasal masses connected with the nervous system is MR.
2. Inflammation:
Acute sinusitis (a.c.) is rather commonly seen as a complication of rhinitis due to a swelling of the endonasal mucosa which obliterates the ostia of

the paranasal sinuses; plain x-ray films of the paranasal sinuses are sufficient to set the diagnosis in most cases. Orbital abscess, however, as a severe complication of a.c. might require further CT investigation (Fig.1). Mucoceles may result from obstruction of a sinus ostium and are most commonly located in the frontal sinuses (Fig. 2). Their origin might be either inflammatory, traumatic or iatrogenic (following extranasal sinus surgery). Continued expansion of the process can lead to an affection of the adjacent structures (rarification of bone, expansion into the orbit resulting in proptosis). CT examination will show mucoceles as expansile lesions causing distention and erosion of bones; usually, however, they will not reveal the extensive bone destruction seen in malignant tumors. Mucoceles do not show enhancement after the application of contrast media (C.m.); however, in case of infection (pyocele) an uptake of c.m. will be seen.

Nasal polyps usually originate from the ethmoid sinuses, grow towards the nasal cavity and may lead to a complete obstruction of the nose and paranasal sinuses. They show a moderate contrast enhancement on CT. As nasal polyps are likely to recur after surgical removal, a coronar CT-scan should be performed in order to evaluate the ethmoid roof for osseous defects (Fig. 3).

3. Trauma:

In most facial injuries plain x-ray films are adequate to investigate the extent of the fracture. In case the patient has suffered severe trauma of the head, however, a CT-evaluation is mandatory to rule out cerebral injury. Additionally, CT-scanning will be helpful in the diagnosis of fractures of the anterior skull base, becauses clinical signs (CSF-rhinorrhea) might be absent or not detectable in the acute trauma patient. Overlooked fractures might lead to life-threatening complications like meningo-encephalitis or brain abscess.

Even though, patients with osseous destructions mostly present with extensive facial skin and soft tissue lesions (Fig. 4), fractures of the anterior skull must also be excluded, if only minor signs of soft tissue injuries are visible (Fig. 5).

For complete evaluation of the anterior skull base, axial and coronal scans should be taken. Unfortunately many trauma patients arrive at the Emergency Unit intubated and in a very poor condition; in most cases they do not tolerate the hyperextension maneuver, which is necessary to receive the coronal plane. In these patients, the ethmoid roof, which is the weakest point of the anterior skull base and therefore most likely to be involved in a fracture, cannot be examined properly.

4. Neoplastic lesions:

In tumors of the nose and paranasal sinuses, clinical symptoms (i.e. congestion of the nose, epistaxis, facial swelling, displacement of the eye etc.) often appear at an anvanced stage. If a tumor is suspected, a CT evaluation should be performed immediately to investigate the extent, localization and possible grade of infiltration of the tumor towards the surrounding tissue (bone, anterior cranial fossa, infratemporal and retromaxillary space). Conventional radiographs are usually not capable to supply adequate information.

Basically a tumor must be suspected, if soft-tissue tumor mass can be visualized on CT. In fact, however, there is as wide variety of different possibilities that might be responsible for this feature, ranging from polyps or mucoceles to benign or malignant tumors of different histologic

pattern.

Changes in the adjacent bones (destruction or remodelling) are possible, but not imperative, appear in benign as well as in malignant tumors, polyps or mucoceles and might aid in the differential diagnosis of nose and paranasal sinus tumors. Another important differentiation-criterion is the uptake of contrast medium, which varies from marked enhancement in some kinds of sarcomas to minimal or no enhancement in squamous cell carcinomas (Som 1985); the latter histological type accounts for 80%-90% of malignancies in the nose and paranasal sinuses (Carter 1988).

Summing up our findings, it can be confirmed that CT is still a sufficient diagnostic tool in the evaluation of the nose and paranasal sinuses. Even though MR might supply equivalent or even better information in the differential diagnosis of tumors in this area, CT examination remains mandatory if an affection of adjacant osseous structures, particularly the anterior skull base, is in question. The decision, whether the skull base has been eroded already, can be of great importance for the therapeutic approach. In trauma patients, CT is still the radiologic tool of choice.

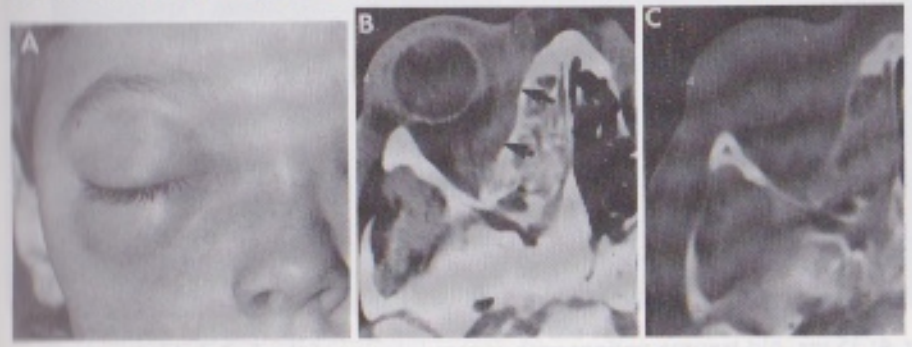

Fig.1: orbital abscess in a 8 yrs. old boy (A). The soft tissue window (B) shows the inflammatory reaction inside the right orbit (arrow); the bone window reveals no bulging of the lamina papyracea (C).

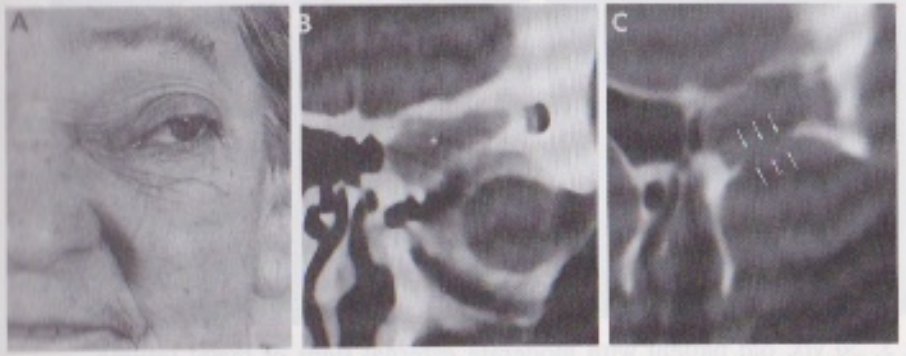

Fig. 2: 78 yrs. old female with lateral displacement of the left eye due to a large mucocele of the left frontal sinus (A). The mucocele has already expanded into the left orbit (B); the bone window (C) confirms that the superior medial wall of the orbit has been eroded by the mucocele (arrows).

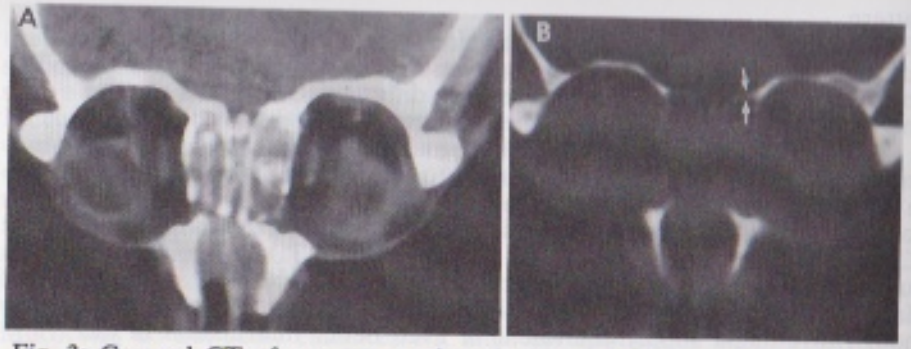

Fig. 3: Coronal CT of recurrent polyposis. The soft tissue window (A) reveals the obstruction of the nose and ethmoid by the an extensive mass of polyps. The osseous defects (arrows) in the left ethmoid roof become obvious in the corresponding bone window (B).

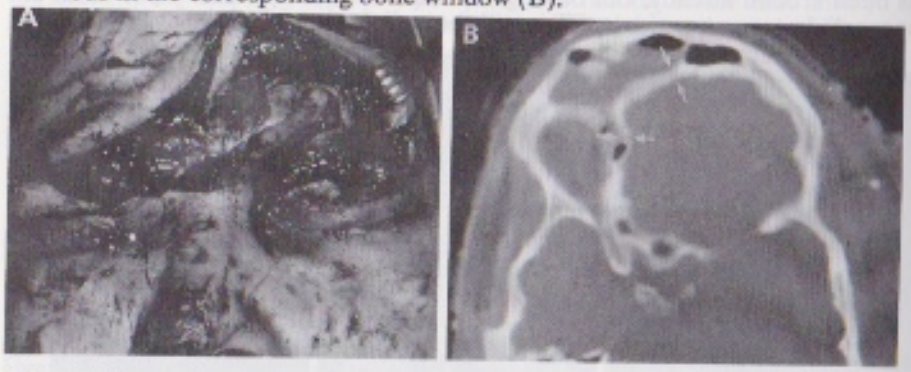

Fig. 4: 35 yrs. old trauma patient with severe injuries of the facial skin and soft tissue (A). The axial CT scan (B) reveals multiple fractures of the anterior skull base (arrows).

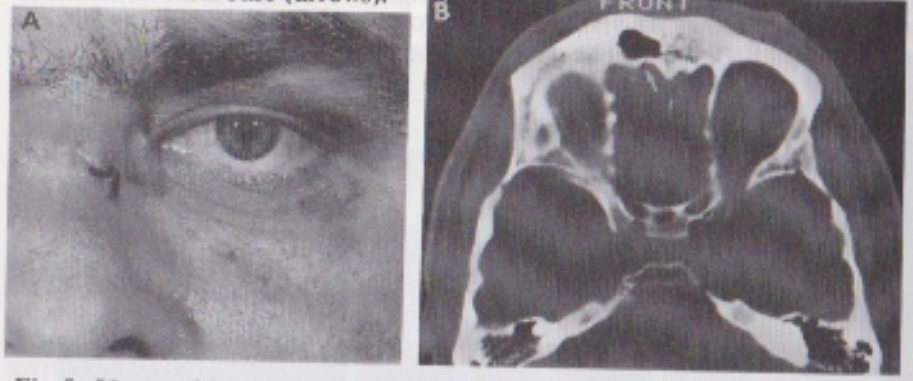

Fig 5: 50 yrs. old patient with moderate external signs of facial trauma (A). After persistent CSF-rhinorrhea he underwent CT-examination ("high-resolution"-technique). The axial bone window scan revealed a fracture in the posterior wall of the left frontal sinus (B). Note the presence of an intracerebral air bubble (arrow).

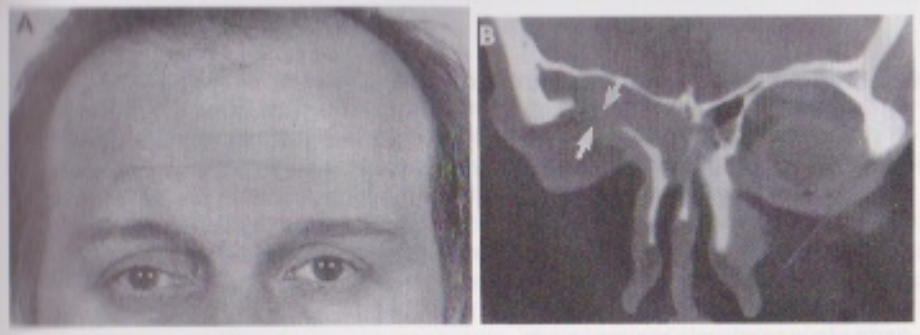

Fig. 6: 45 yrs. old patient (A) with moderate lateral displacement of the right eye due to a paranasal sinus neoplasm (adenocarcinoma). The coronal plane (B) reveals the destruction of the medial parts of the orbital roof (arrows).

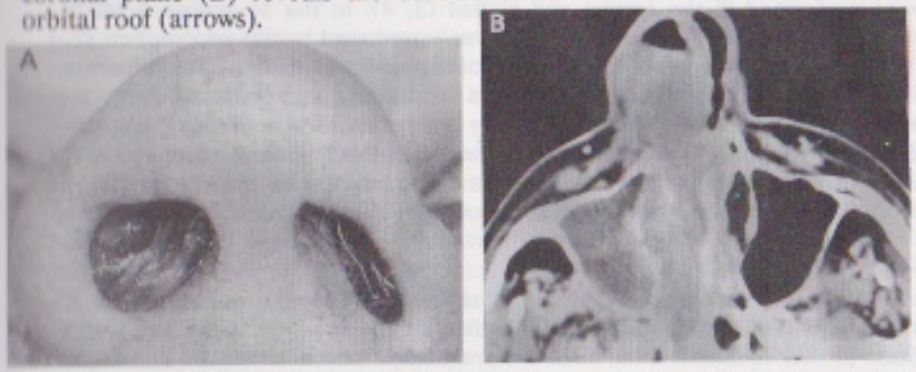

Fig. 7: 80 yrs. old patient with a melanoma of the right nasal cavity, which has eroded the lateral nasal wall, thus protruding into the right maxillary and ethmoid sinuses. The tumor has bulged the right nostril (A). Coronar CT scan (soft tissue window) reveals a complete obstruction of the right nasal cavity and paranasal sinuses (B), which is due to tumor tissue in the ethmoid and maxillary sinuses.

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Ultrasonography of Paranasal Sinus Lesions

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Early investigations to examine the paranasal sinuses using ultrasonography were performed in the forties and sixties (3, 4). In the seventies A-Mode examination of the paranasal sinuses was introduced in clinical practice (2, 5). It soon became a routine tool in clinical diagnosis of paranasal sinus disease. Today modern equipment allows reliable and easy to handle A-mode-ultrasonography of the frontal, maxillary and ethmoid sinus. With the introduction of real-time B-mode ultrasonography, better visualization of the soft tissue overlying the pneumatized cavities of the facial skeleton, abnormalities of bony structures and paranasal sinus content is feasible.

A-SCAN

In A-mode ultrasonography changes in acoustic impedance yield peaks on a one-dimensional (time) axis corresponding to the distance from the ultrasound-probe. To examine the three-dimensional paranasal sinus, the investigator must realize the depth of the sinus under investigation and take variations of the form and volume into consideration. It should be memorized, that in adults the distance from the surface of the skin to the posterior wall of the maxillary sinus is approximately 5 cm, for the frontal sinus approximately 3 cm and for the ethmoid sinus approximately 6 cm. A 3.5-5 MHz-probe is coupled to typical anatomic sites of the midface (7), corresponding to the deepest diameter of the paranasal sinus under investigation (Fig. 1). Than the probe is moved over the anterior wall of the sinus (arrows) to scan the whole cavity for disease. In the healthy, air containing sinus, total sound reflection occurs at the mucosa-air interface due to the sudden change of acoustic impedance. This yields a steep peak about 1 cm from the transducer. No further signals can be obtained from deeper structures. Only pathological changes within the sinus, e.g. secretion, mucosal swelling, blood or tumors yield deeper penetration of the sound waves and corresponding signals. If the sinus is filled with sound conducting material, a typical back-wall echo occurs due to sound reflection at the posterior bony wall. Two methods of investigation are to be distinguished, the biometric method, which allows to determine the distance from the surface of the skin to the back-wall echo of the diseased sinus and the so called dynamic technique. Using this technique, the examiner simultaneously changes the head-position of the patient and the amplification of the receiver. The synthesis of these two procedures allows sophisticated evaluation of paranasal sinus disease.

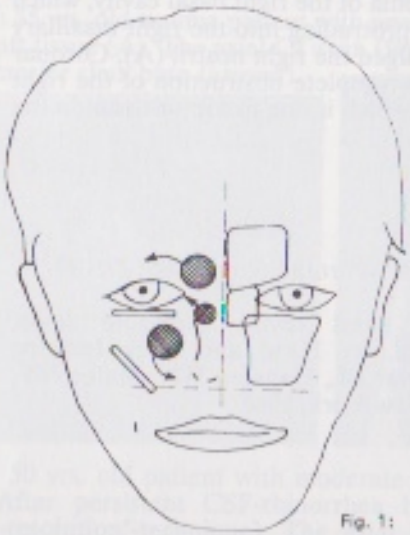

Fig. 1:

In the hands of a skilled examiner, A-mode ultrasonography is a quick, reliable method without adverse effects. It can be repeated ad libitum. Compared with other imaging techniques, the liability of A-mode ultrasonography for diagnosing paranasal sinus disease was found to be approximately 90%. Most accurate results were obtained in normal, air containing sinuses, in acute sinusitis and in mucosal thickening of more than 3 mm. Isolated cysts or polyps within the alveolar recessus may remain undetected, when they have no contact with the anterior wall of the sinus. Pathological changes at the posterior wall or roof of the sinus can not be visualized, when sound conduction is prevented by interposed air.

Following Caldwell Luc operation, sinus radiograms reveal total opacification in about 40%. A-mode ultrasonography is a valuable tool to differentiate between air, fluid or scar-tissue within the operated sinus due to the pattern of the reflected sound waves. In combination with standard sinus x-rays A-mode ultrasonography gives additional information about the pathological sinus content.

Concerning the skills of the examiner and the diagnostic value of the technique, most reliable results using A-mode ultrasonography are obtained examining the maxillary sinus, followed by the frontal sinus and the anterior ethmoid sinus. Evaluation of the posterior ethmoid and the sphenoid sinus through the eye is difficult and not reliable enough for routine-examination.

In combination with the history and clinical examination, A-mode ultrasonography is a valuable and reliable tool in diagnosis of sinusitis and in follow up examinations. It has it's great merits in examination of the paranasal sinuses in children, when little pneumatization yields unreliable results in standard x-rays (8). During pregnancy and following radical maxillary sinus operation, it is the method of choice to examine the paranasal sinuses.

B-SCAN

Although modern real-time B-scanners do not allow better axial and lateral resolution than A-scanners, their advantages are obvious. The two-dimensional visualization of a three-dimensional structure allows better topographic orientation and facilitates interpretation. Due to the small dimensions of the anterior wall of the sinuses as compared with the size of the transducers

used, it might be difficult to couple the probe to the soft tissue surface overlying the sinus. This is especially true in infants. However, using sector-scanners or small parts probes it is almost always possible to examine the paranasal sinuses and the overlying soft tissue structures in adults. First axial scans though the sinus under investigation are obtained in the sitting patient. Then vertical scans are obtained to verify the findings. For examination of the maxillary and ethmoid sinuses both sides are compared including parts of the orbital content in axial and vertical sections to visualize the bony limits of the sinus. It is important to examine the floor of the orbit and the lamina papyracea, especially when orbital structures are involved in inflammation, trauma or neoplasms. To examine the frontal sinus, either a sector scan is placed directly over the nasion to simultaneously visualize both sinuses or vertical scans are made including parts of the orbit. While examination of the posterior ethmoid or sphenoid sinus is not reliable using A-scans, pathological changes within these sinuses can be detected using B-scan-examination.

Normal, air containing sinuses:
In the normal maxillary sinus only the anterior bony wall and the overlying soft tissue can be visualized. Due to total sound reflection at the air-mucosa interface in the normal sinus, deeper structures are beyond the scope. In vertical scans the orbital content is seen and behind the anterior wall of the maxillary sinus, there is an echo-free space.
Scanning the normal frontal sinus, both anterior walls and the overlying tissue are seen, neighbored by the cranial bone on both sides. The sinus content and the posterior wall can not be displayed.
Scanning the ethmoid sinus axial scans are preferred. Visualization of the orbital content facilitates orientation. Medial to the eye the lateral wall of the nose is displayed, while the normal, air containing ethmoidal cells are not seen. The normal sphenoid sinus can not be visualized using B-scan.

Inflammatory changes:
Inflammatory changes of the maxillary sinus are associated with accumulation of secretions or mucosal thickening and allow sound conduction through the cavity and visualization of the posterior wall. In children, the posterior wall may be U-shaped and lie within varying distances from the probe. In adults the posterior wall is normally V-shaped and the echo is found approximately 5 cm from the transducer. In axial scans a typical posterior recess is seen. The zygomatic recess causes a lateral expansion of the displayed sinus. It is rarely possible to visualize the medial and lateral wall simultaneously. To scan the medial wall, the probe must be tilted medially, to scan the lateral wall it must be tilted laterally. Multiple echoes within the sinus may appear according to the inhomogeneity of the sinus content. They must be differentiated from reverberations. In vertical scans the distance to the back-wall echo decreases from the floor of the orbit to the alveolar recess. The floor of the orbit and parts of the orbital content are adequately displayed.
Inflammatory changes of the frontal sinus allow visualization of the posterior wall, appearing as a brilliant white echoline approximately 1.3-3 cm from the probe. Mucosal swelling or secretions reveal multiple echoes within the sinus. Scanning the inflamed ethmoid sinus, bony septa and cells with echogenic content may be seen medial to the orbital content. Orbital complications like a subperiosteal abscess may be visualized due to the elevated periorbit (1). The infected sphenoid sinus can sometimes be visualized medial and posterior to the orbital apex. Inflammation of the posterior ethmoid facilitates scanning the sphenoid sinus.

Traumatic changes:
Following trauma, the normally 0.8 to 1 cm deep soft tissue layer over the anterior wall of the maxillary sinus is thickened due to hematoma. Fractures of the anterior or lateral wall appear as dehiscences in the corresponding bright echoes. The axial scan may reveal highly echogenic blood clots and sometimes prolapsing orbital tissue is visualized.
The traumatized frontal sinus may reveal soft tissue swelling overlying the anterior wall and bony dehiscences of the anterior wall. In the blood filled sinus, the posterior wall may be visible and scanned for bony dehiscences.

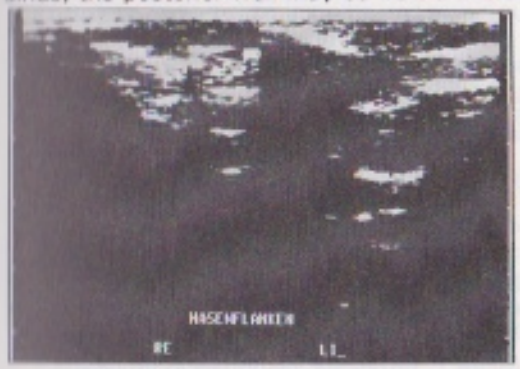

Fig. 2: Right nasal bone fracture (arrow)

In the traumatized ethmoid, pathological sinus content might be seen. Fractures of the lamina papyracea are rarely diagnosed by B-scan ultrasonography due to insufficient lateral resolution.
B-mode ultrasonography is a valuable tool to visualize nasal bone fractures in children. Using a soft waterpad or a sufficient amount of coupling gel, both nasal bones and frontal processes can be visualized in horizontal and vertical sections. Fractures appear as dehiscences in the bright echoline representing the nasal bones (Fig. 2).

Tumors:
Neoplastic disease share common ultrasonographic features in all paranasal sinuses. Destruction of the bony wall, high echogenity and invasion of the orbit are suspicious (6). B-scan ultrasonography allows good differentiation of retrobulbar fat, ocular muscles and tumor invading the orbit (9). Tumors of the sphenoid are normally not visualized with sufficient accuracy.
Mucoceles of the paranasal sinuses are diagnosed with high reliability. The axial scan reveals echopoor structures within the cavity, often with ballooning or destruction of the bony walls of the sinus.

Soft tissues of the facial skeleton:
Inflammatory and tumorous changes of the soft tissue of the face can be ideally visualized using B-scan examination. Simultaneous sonography and

palpation yields information about consistency, mobility, compressibility and possible bony invasion. Foreign bodies are easily detected, even when they are non-radiogenic. Ultrasonographic guided fine needle biopsy of structures situated within the soft tissue or within the paranasal sinuses offers new options to gain a cytologic or histologic diagnosis. This allows for definite diagnosis.

Ultrasonography does not allow routine preoperative evaluation of the bony anatomy of the paranasal sinuses and therefore it is not able to replace computed tomography in preoperative management of paranasal sinus disease. However, it is an excellent tool in daily routine and follow up examinations. Combined with clinical findings it offers valuable additional information about paranasal and viscerocranial soft tissue disease and is the method of choice to control harvesting of cytologic or histologic specimens preoperatively. In the hands of the skilled examiner it is a costeffective, accurate and innocuous instrument for diagnosis of various pathologies in the paranasal sinuses and the soft tissues of the facial skeleton.

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Merit and Demerit of Endoscopic Surgery

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Endoscopic endonasal sinus surgery can look back on 15 to 20 years of successful application in different techniques and today it has become a standard therapeutic modality in the field of rhinosurgery. This period of time might suffice to compile a first comprehensive resumé of the merits and demerits of endoscopic endonasal surgery. By **"Merits"** we mean the **benefits** of this type of surgery for patient and surgeon alike.

Functional endoscopic sinus surgery comprises a system of surgical steps aimed at treating more or less circumscribed chronic paranasal sinusitis through the endonasal route under the guidance of an endoscope. This step by step surgical process concentrates on the key area of the middle nasal meatus and is adapted to the individual pathophysiology and pathological microanatomy of the patient. It is thanks to rhinologists such as Messerklinger, Stammberger, Kennedy, Rice and Schaefer, Wigand and many others that comprehensive, detailled descriptions of this surgical technique have recently been published. Functional endoscopic and endonasal sinus surgery has the unquestionable **benefit of a maximal protection of the external skin, oral mucosa and the bony frame-work of the face and sinuses, as well as of the respiratory and olfactory mucosa.** Even if we leave aside the pathophysiological errors made during external approaches, with their detour to the key areas of the inflammatory diseased paranasal sinuses, and the misleading concept of radical mucosal removal, we have to admit, that the transoral surgical access itself leaves the patient with a specific morbidity such as facial asymmetry and paresthesia in at least 10 % of all cases according to Defreitas and Lucente (1988). The external scars caused by a transfacial approach were criticized as beeing disfiguring in 10 % of all cases according to Meier and his coworkers in 1991.

The main indication for endoscopic endonasal surgery up to now has always been **chronic ethmoiditis and chronic maxillary sinusitis.** Numerous, important statistics on the results of such surgery have been made over a longer period of observation and are already available

(e.g. Stammberger 1991). In our hands, treatment of chronic diffuse ethmoiditis had been successful in 82 % of the cases (Wigand 1990). A less favorable outcome of surgery in individual cases strongly depends on specific factors, the most important one beeing analgesic intolerance.

Moreover, besides the overall subjective assessments of all the patients, we now are able to offer those **patients with bronchial asthma or with an impaired sense of smell** a therapy with a respectable percentage of specific improvements. 78 % of the patients with an impaired olfactory function showed a marked improvement after surgery. Using lung function tests pre- and postoperatively, we examined the influence of endonasal surgery for chronic diffuse ethmoiditis on 13 patients with asthma and on 4 other patients with bronchial hyperreactivity, but without manifest asthma. In those 4 patients, bron-chial hyperractivity disappeared after surgery, wheras five asthmatics could stop the medication of one to three drugs. Five others were able to reduce the dosage of one of their drugs by 50 % or more. Lung function and medication remained unchanged in two asthmatic patients, one patient had an unchanged lung function due to addition of 1 drug. In conclusion, we could show that endoscopic endonasal surgery is able to improve the antiasthmatic therapy to a considerable degree (Hosemann et al. 1990).

The efficiency of endoscopic surgery has also been con-firmed by **endonasal treatment of the naso-lacrimal duct**. All in all, 86 % of our patients suffering from a complete stenosis of the lacrimal duct felt excellent and another 9 % improved after endonasal dacryocystorhinostomy (N=56). Even surgical revision was successful in 82 % of the cases.

Apart from the usual chronic-diffuse, hyperplastic ethmoiditis and lacrimal stenosis, the experienced surgeon may even **extend the indications for endoscopic surgery** to many benign and a few malignant **tumors of the nose and the paranasal sinuses**. Many **inflammatory complications of paranasal sinusitis, isolated diseases of the frontal sinus**, as well as **dysthyroid orbitopathy** (Kennedy et al. 1990) can be dealt with endonasally in the same manner. Even the **external access e.g. in traumatology can be reduced in extent** by endoscopic techniques.
In the last 2 years, 26 patients diagnosed as having mucopyoceles or destructive empyemas of the frontal sinus were subjected to endoscopic endonasal surgery. 18 patients with a follow-up exceeding 3 months could be reexamined after surgery. Patient`s opinion was excellent or good in 16 patients. Using endoscopy the frontal sinus access proofed to be open wide in 5 patients. A smaller but sufficient frontal ostium could be achieved in another 8 patients. Similar reports to this type of surgery had been given by Kennedy and coworkers in 1989, as well as by Perko in the same year.

Some tumors may be operated on by the endonasal route, too. According to our report of 1990 (Waitz and Wigand) 35 out of 51 patients with inverted papillomas of the nose and paranasal sinuses could be treated by the endonasal surgical route. Endoscopic surgery proved to be successful even in large lesions affecting the posterior ethmoid, the sphenoid sinus or the region of the nasolacrimal duct. We have a smaller list of malignant tumors, which have been refered to endonasal, endoscopic surgery in the last two years (2 carcinomas, 2 sarkomas, 1 malignant histiocytoma, 1 esthesioneuroblastoma; postoperative follow-up 11-24 months).

Small and middlesized CSF leaks as a complication of endonasal endoscopic surgery may be immediately closed while maintaining the endonasal approach. Provided that one has not invaded the intracranial space with an instrument and has not damaged brain tissue or its vessels, this complication loses its frightening aspect for both patient and surgeon by the use of an endoscope and an autologous mucosal transplant. We have reexamined 18 patients with a circimscribed (posttraumatic or iatrogenic) cerebrospinal fluid leak after endonasal-endoscopic repair using autogenous grafts of conchal mucosa at an average of 17 months postoperatively. No liquorrhoe, meningitis or cerebral abscess had to be observed postoperatively (Hosemann et al. 1991).

The extension of indications for endonasal surgery with its reduced specific morbidity for the patient should in our opinion cause an **increase in compliance or acceptability** not only on the part of the patient. The overall increased acceptability for the patients allows us to offer help to many new patients **in collaboration with other specialists.**

The benefits of endoscopic surgery can be achieved only by an assured mastery of the technique and the local microanatomy. At the same time this is the most important **demerit**, that means **limitation** of this kind of surgery. Many malignant and some benign tumors evade endonasal endoscopic surgery, as do some of the life-threatening inflammatory complications. The endoscopic opening-up of the frontal sinus alone does not always suffice to bring about a healing of the more deeply hidden recesses of the sinus.
During the last 3 years we have been asked to give an expert report in court in 9 cases of life-threatening **complications** resulting from endonasal surgery which

had occured elsewhere in Germany. One aditional fatality happend to occur in our clinic in 1988. Of course, these numbers do certainly reflect the substitution of transoral and transfacial surgery by endonasal techniques in the field of chronic paranasal sinusitis. Any catastrophic outcomes in individual cases of endonasal endoscopic surgery should not be accepted as an adequate counterweight to the benefits of this type of surgery for thousands of our patients. Not even older statistics on transfacial and transmaxillary ethmoidectomies are able to exclude the possibilities of serious complications in up to 1 % of the procedures. The fatalities pinpoint the challenge presented to all rhinologists entering the field of endoscopic surgery to undergo continuing education in pathophysiology and microanatomy and subject themselves to conscientious decision-making before and during surgery as an absolute priority.

Using the image of weighing up the **benefits and limitations** of this type of surgery and summarizing the data presented, we would like to show unbalanced scales in favor of the endoscopic endonasal surgery. We expect that progressive operative experience, together with the development of new instrumental equipment and in particular a better understanding of sinus pathology will, in the future, shift the balance of merits and demerits in endoscopic surgery further towards the benefits.

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TECHNICAL PROBLEMS IN ENDOSCOPIC SINUS SURGERY

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INTRODUCTION

Theoretically, the excellent visualization and magnification possible with endoscopes should enhance the safety of ethmoidectomy. However, as physicians adapt to the new technique, there are reports of series with high complication rates (Stankiewicz, 1987; Stankiewicz, 1989; Maniglia, 1991). The purpose of this paper is not to detail the surgical procedure which has been described elsewhere (Kennedy, 1985; Stammberger, 1986) but rather to review some of the concepts, misconceptions and technical problems associated with the functional endoscopic approach. Basic principles which enhance safety in the surgical procedure are re-emphasized. The term functional endoscopic sinus surgery was originally developed by Kennedy *et al.*(1985) to describe an approach to inflammatory sinus disease utilized by Messerklinger. However, it is frequently forgotten that the primary aspects of this approach are theoretical and diagnostic and the surgery is purely secondary. The basic premise of the technique is that ostiomeatal obstruction is a major event in the pathogenesis of inflammatory sinus disease and that infection is secondary to this and typically reversible when the ostiomeatal problem is corrected.(Kennedy *et al.*1985)

However, it must be also recognized that, although the final common pathway in the disease process is ostiomeatal obstruction, the underlying etiologies of inflammatory sinus disease are multifactorial. Potential etiologic elements include environmental, immunologic and possibly genetic and stress factors. Additionally, the disease is frequently associated with an overall mucosal hyper-reactivity which may require long term medical therapy. Careful endoscopic follow up is therefore stressed. Indeed it well recognized that persistent sinus disease may remain asymptomatic for many years (Neel *et al.*1987) A second basic premise therefore is that subsequent therapy should be based on objective endoscopic findings. Limited persistent or recurrent disease is treated before it again becomes symptomatic.

Meticulous diagnosis by endoscopy and, when necessary, computed tomography (CT) are a prerequisite of this technique.(Zinreich *et al.*1987) Although endoscopic surgical techniques can also be used for the treatment of diffuse sinonasal polyposis, the real advantage of this technique occurs when careful diagnosis reveals a limited underlying cause for diffuse disease and this limited underlying cause can be corrected by a minor surgical procedure, thus dramatically reducing patient morbidity.

There are two commonly held misconceptions about endoscopic sinus surgery. One is that the use of endoscopes will enable a surgeon with limited ethmoid experience to performed the surgery safely. A second is that use of endoscopes is inherently dangerous. Neither is true. Ethmoidectomy is a procedure with potential serious and even fatal complications. Safety can only be enhanced with excellent training, familiarity with the anatomy and adherence to certain technical precepts.

TECHNIQUE

Reduced visualization resulting from bleeding is a common denominator in many complications arising from ethmoidectomy. In order to minimize the problem, careful attention to detail is required both preoperatively and intraoperatively. Prior to surgery, inflammation can be minimized by restarting patients on antibiotics 1-2 weeks preoperatively. Patients with diffuse polyposis or with hyper-reactive nasal mucosa should be restarted on oral steroids several days prior to surgery. Patients on oral steroids for asthma should have the dosage increased for several days preoperatively, both to shrink the polypoid disease and to improve bronchial stabilization.

Endoscopic sinus surgery is most safely performed under local anesthesia. Bleeding is minimized and the inherent sensitivity of the medial orbital wall and skull base in the region of the anterior and posterior ethmoidal vessels provides the surgeon with a warning if the surgery encroaches upon these areas. Additionally, should the surgery result in an intraorbital hematoma, the surgeon is able to monitor the patient for possible visual compromise.

Topical cocaine powder on nasal applicators applied to the regions of major neurovascular supply is the method of topical anesthesia preferred by the author. However, a mixture of pontocaine and oxymetazoline may also be utilized. After topical anesthesia has been achieved, the lateral nasal wall is injected with 1% xylocaine with 1:100,000 adrenaline. In order to minimize trauma, the application of anesthesia is performed entirely under endoscopic control. Injection sites are carefully chosen that the number of sites is minimized and to ensure that they do not lie in the immediate path of the lens of the endoscope. In addition to injecting the lateral nasal wall anteriorly, injection of the postero-inferior middle turbinate and trans nasal injection of the sphenopalatine ganglion are helpful. The latter is performed with an angled needle directed postero-laterally through the inferior aspect of the ground lamella.

The availability of a coronal CT or of AP polytomograms in the operating room is essential. These should be reviewed in an organized fashion while the anesthesia takes effect. The height and slope of the ethmoid roof and its thickness in different areas are again analyzed. The shape of the medial orbital wall is reviewed and the presence of atelectatic infundibulum excluded. The vertical distance between the maxillary sinus and the ethmoid roof in the posterior ethmoid is also reviewed. Within the sphenoid sinus, the extent of pneumatization, the relative positions of the carotid arteries, the intersinus septae and the optic nerve impressions are all noted. Anteriorly, the difficult anatomy of the frontal recess is again scrutinized.

All patients are provided with intravenous analgesia and monitored by an anesthesiologist. Music provided through headphones adds to patient relaxation. In order to maximize instrument control, the surgery should be performed with the surgeon seated, resting the elbow holding the endoscope on a Mayo stand and stabilizing the hand holding the endoscope against the patient's face.

Several important intraoperative principles can enhance the safety of the procedure. First and foremost, great care must be taken to avoid any trauma to the anterior portion of the nose or to the middle turbinate. Minimal bleeding in this area dramatically reduces visualization by continually fogging the endoscope lens. Secondly it is important to remember that it is only necessary to marsupialize disease and remove osteitic bone. Complete ethmoidectomy or sphenoethmoidectomy is not always required. However, two important landmarks, the medial orbital wall and the skull base, must be identified for the safe completion of more than a very limited anterior ethmoidectomy. Finally, disorientation is reduced by the routine use of a 0 degree telescope, at least until such time as the two major landmarks have been identified.

The medial orbital wall should be identified and skeletonized early in the procedure so as to maximize exposure and ensure that any dissection superiorly is performed laterally where the skull base is usually thicker. After performing infundibulotomy and removing the bulla, the posterior ethmoid may be entered when necessary by piercing the ground lamella of the middle turbinate inferiorly and medially. The telescope should always be withdrawn slightly before this procedure is performed so as to re-ascertain relative position to the inferior boarder of the middle turbinate and to the overall nasal anatomy.

The skull base is typically identified within the posterior ethmoid where the cells are larger, the skull base is more horizontal and the disease is typically less marked. Where it cannot be easily recognized it is slowly skeletonized by removing intersinus septae layer by layer from posterior to anteriorly using up-biting forceps. Recognition may be enhanced by visualization of the posterior ethmoid nerve, medial indentations due to olfactory filae or identification of the typical pyramidal shaped last posterior ethmoidal cell. When the bulge of the sphenoid sinus is evident, this sinus may be entered through the posterior ethmoid. It always lies more inferiorly and medially than expected. When the site is in doubt, the ostium is identified medial to the superior turbinate and widened.

After identification of the skull base, angled telescopes may be substituted for the 0 degree. The dissection is carried anteriorly, in a retrograde fashion along the skull base, into the frontal recess. Care is taken minimize mucosal trauma in this area. Identification of the natural ostium of the frontal sinus can be difficult and a supraorbital cell can easily be mistaken for the sinus. Typically the ostium lies more medially and anteriorly than expected. However, it must be remembered that the ethmoidal roof is also thinnest medially in the area of the anterior ethmoidal artery.

The ostium of the maxillary sinus is identified by displacing the cut edge of the uncinate process medially and inferiorly. It may be opened into the posterior fontanelle with scissors and anteriorly and inferiorly with backbiting forceps. It is essential that any middle meatal opening connects with the natural ostium if recirculation of mucus and potential reinfection is to be minimized.

RESULTS

Utilizing these precepts, the senior author has performed endoscopic sinus surgery with a high degree of safety for many years. There have been no cases of intracranial entry, CSF rhinorrhea, intraorbital hematoma, diplopia, visual loss or meningitis. Two patients developed epiphora postoperatively, one of these was related to postoperative division of adhesions and the use of silver nitrate to cauterize the cut edge of the adhesion on the lateral nasal wall. Three patients have required packing postoperatively due to bleeding. One patient early in the series required blood transfusion for postoperative bleeding. This patient also underwent a septoplasty and was packed in the early postoperative period. The bleeding occurred after the packing was removed and was possibly arising from the septum. One patient developed a preseptal orbital bleed during cleaning three weeks postoperatively.

DISCUSSION

Inadequate training and poor visualization due to intraoperative hemorrhage are the most important common denominators in intraoperative complications from ethmoidectomy. Whenever significant bleeding occurs which interferes with visualization and is not controlled by the placement of a temporary packing or hemostatic agent, the surgeon should terminate the procedure. Although currently available suction irrigation handles have been found too traumatic for the functional technique, other supplemental instrumentation may augment meticulous atraumatic technique. Kennedy-Blakesley suction forceps enable the aspiration of blood during tissue removal and minimize the necessity to alternate forceps with suction. The use of a fiber administered KTP-532 laser enables the bloodless removal of massive polyposis by sectioning the polyps at the base.(Kennedy & Zinreich, 1988) More recently, incorporation of the Holmium-Yag laser has enabled both bloodless removal of soft tissue and bone. However, care is required not to heat underlying vital structures. Recent work with an electrically controlled "scope scrubber" has also dramatically reduced the necessity to clean the endoscope lens.

However, adequate care of patients with chronic inflammatory sinus disease requires a great deal more than safe ethmoidectomy. Precise diagnosis and medical therapy based on objective findings as well as upon patient symptoms are essential. Postoperative endoscopic follow up, medical therapy and care of the ethmoid cavity is essential. Following surgery particular attention must be paid to the area of the frontal recess if we are to minimize stenosis in this area and avoid creating the frontal sinus mucoceles of tomorrow.

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ENDOSCOPIC SINUS SURGERY - COMPLICATIONS AND HOW TO AVOID THEM

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COMPLICATIONS

Providing the necessary steps are taken to ensure that as much information regarding the anatomy and pathology of the individual patient is acquired prior to endoscopic sinus surgery, complications, in experienced hands, should be few. Notwithstanding this, complications can and do occur and these can be considered under three headings:-

1 INTRACRANIAL
- cerebrospinal fluid (CSF) rhinorrhoea
- intracranial bleeding
- meningitis
- brain abscess.

2 OPHTHAMIC
- haematoma
- surgical emphysema
- damage to the naso-lacrimal sac or duct
- diplopia
- blindness which may be due to direct damage to the optic nerves or indirectly due to increased intra-orbital pressure secondary to bleeding

3 INTRA-NASAL
- haemorrhage which may be a diffuse general ooze or related to a specific artery such as the anterior ethmoidal, spheno-palantine or carotid,
- anosmia or hyposmia with associated ageusia
- adhesions which may cause blockage of the osteomeatal complex or nasal obstruction.

Most patients have little in the way of post-operative mobidity but some will complain of facial pain or headache, mucopurulent rhinorrhoea, cachosmia and

some crusting during the early post-operative period.

In a personal series of a little over 600 cases reviewed retrospectively, there have been 13 cases of orbital haematoma, one of which was severe enough to require an external ethmoidectomy and decompression, the remaining 12 were minimal affecting the medial border of the lower eyelid and resolved within 2 weeks without further complication. Three cases have required transfusion, 2 of which had cystic fibrosis, with poor liver function. There were no cases of blindness, diplopia, CSF leaks or other intra-cranial complication. In a series of 181 cases studied prospectively, 37 were complicated by the formation of synechiae, most of which resolved following treatment at the first or second post-operative visit. Nine cases experienced post-operative bleeding sufficient to require either packing or at least over-night observation. Two patients required extended admissions to control exacerbation of their pre-existing asthma.

In a series of over 4000 patients, Stammberger and Wolf (1988) reported only two cases of cerebrospinal fluid rhinorrhoea, no intracranial complications and no ophthalmic complications. Wigand (1990) reporting on 220 patients undergoing 'complete ethmoidectomy' reported: asthma attack immediately post-op 4 (1.8%) neuralgia of face and head 4 (1.8%), post-op anosmia 2 (0.9%), CSF leak 2 (0.9%), orbital haematoma 1 (0.5%), ethmoid mucocoel 1 (0.5%), there were no deaths, cases of blindness, diplopia, meningitis or ozoena.

The complication rate decreases with increasing experience and this 'learning curve' was illustrated by Stankiewicz (1989) who reported a complication rate of 29.0% in the first ninety cases he performed compared with only 2.2% in the next ninety. Most of the complications were minor such as adhesions and closure of the antrostomies but there were 2 cases of CSF rhinorrhoea and one case of temporary blindness. Complications may occur with conventional ethmoidal surgery and Maniglia (1989) reported thirteen patients with complications following intra-nasal ethmoidectomy: seven cases of blindness, four CSF leaks and two deaths, while a 2.8% complication rate for this operation was reported by Freedman and Kern. (1979)

AVOIDING COMPLICATIONS:

1 PRE-OPERATIVE ASSESSMENT

Despite the advances in endoscopy and imaging, it is still as important as ever to take a thorough history. Is the patient known to have a bleeding disorder, or is there any family history of such ? Does the patient have asthma ? Is there any known sensitivity to drugs, in particular is the patient sensitive to aspirin ?

The answers to these and similar questions may prevent a complication occurring.

Nasal endoscopy allows the accurate assessment of disease and anatomical abnormalities. The nose should be examined with a speculum in the first instance, however, as it is easy to miss a deviation of the septum particularly when using an endoscope with a wide-angled lens. The orifice of the naso-lacrimal duct can usually be visualized under the inferior turbinate. The posterior choanae, postnasal space, eustachian tube orifices, hiatus semilunaris, infundibular opening, accessory ostia and very occasionally the natural ostium of the maxillary ostium together with the ostium of the sphenoid sinus can all be examined and any unusual anatomy or pathology diagonsed prior to any surgical procedure being undertaken. Endoscopic sinus surgery may, as yet, not be undertaken by all otorhinolaryngologists, but it is probable that nasal endoscopy in the out-patient environment will become routine.

Another major advance in the pre-operative assessment of patients undergoing sinus surgery, has been the introduction of CT Scanning for the investigation of inflammatory disease of the nose and sinuses. This is important, not only to assess the pathological changes, but also to visualise the anatomy and in particular any anomalies such as a dehiscent carotid artery in the sphenoid. This could avoid a most hazardous complication which can often prove fatal. The optic nerve may at times be dehiscent in the sphenoid sinus or be visible in the posterior ethmoids. The slope of the roof of the ethmoids is another useful piece of information, as a steeply sloping roof can easily be penetrated medially. This type of information is often sufficient to put off the less experienced surgeon about to embark on endoscopic surgery, however this knowledge is surely all the more important if the surgeon is about to undertake an intranasal ethmoidectomy with a standard speculum and headlight !

A total "white-out", on CT scanning, where there is pan sinus disease, as may be seen in a patient with massive polyposis, is usually associated, not only with more difficult surgery but is also potentially more hazardous. A little air at the periphery will show up as a "black halo", with air in the frontals, at the roof of the ethmoids, in the sphenoid and possibly in the maxillary antra. The surgeon can expect to reach healthy mucosal lining well before reaching skull base and other vital areas. This sign is associated not only with less treacherous surgery but also with a better prognosis.

2 GOOD FIELD OF VISION

In order to avoid complications it is essential to have a good field of vision. This may be achieved in a variety of ways but the endoscope undoubtedly affords the surgeon with an exceptionally clear field of vision. Initially, a zero degree

endoscope should be used during surgical procedures, reserving the angled telescopes for inspecting recesses,to avoid disorientation.

Reducing bleeding is of paramount importance during endoscopic sinus surgery. Pre-operative treatment with decongestants and local infiltration with vasoconstrictors can minimise this. Local anaesthesia as compared to a general anaesthetic, is said to reduce bleeding though many surgeons in the United Kingdom still prefer the latter in combination with the application of Moffetts solution in the anaesthetic room (1941). It is argued that local anaesthesia is safer, as the patient will experience pain as soon as skull base, optic nerve and other sensitive areas are approached.

If bleeding persists, the use of Kennedy suction forceps, or the suction/irrigation device introduced by Wigand (1990) can be extremely useful.

3 CONSERVATIVE SURGERY

Functional Endoscopic Sinus Surgery (FESS) was a term introduced by Kennedy (1985) to describe the Messerklinger technique (1978), which aims at restoring the natural mucociliary clearance mechanism, drainage and aeration of the sinuses by a minimally invasive technique maintaining as much of the normal anatomy as possible. The surgery commences anteriorly and progresses posteriorly, superiorly and laterally, but only as far as necessary, concentrating particularly on the osteomeatal complex, the anterior ethmoid, its infundibulum and the middle ethmoids. The sphenoid, posterior ethmoids and frontal sinuses are less frequently involved in inflammatory disease than the anterior and middle ethmoids and it is in approaching the most posterior and superior sinuses that one is more likely to encounter complications. By commencing surgery anteriorly and progressing posteriorly, only as far as dictated by the extent of the disease, one should minimise these risks.

4 ADEQUATE TRAINING

As with otological surgery, there can be no substitute for adequate training and cadaver dissection. There are now numerous courses around the world offering excellent tuition and facilities for cadaver work. In most hospitals however, it should be possible to undertake cadaver work and encouragement should be given to junior staff to carry this out on a regular basis.

Another important teaching aid is the video camera. This not only allows the less experienced observer to learn from "the master", but just as importantly, for the more experienced staff to monitor the novice, particularly in the early days.

The video camera does have another advantage, in that the assistant (nurse) can be more involved in the procedure and therefore better able to assist. As

yet, in the United Kingdom, we have not reached the stage where every procedure needs to be video recorded for medico-legal reasons, but this too may become routine in the future.

5 FOLLOW-UP

If in doubt, STOP ! This has to be the most important single rule, if complications are to be avoided. Although the endoscope may be employed to deal with potentially dangerous conditions in the sinuses, for the most part, endoscopic sinus surgery is being undertaken for benign disease. It is therefore all the more tragic when serious complications develop. If the field of vision becomes obscured by bleeding, stop. If one is not quite sure whether this is skull base or not, stop, assume that it is. The great advantage of the meticulous follow-up which has been advocated with this approach, is that the procedure may be completed, under local anaesthesia in the follow-up situation, when it may become obvious, once there is no bleeding, that there is another cell to open, or another polyp to remove. It is this approach which should result in safer surgery and less complications.

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Postoperative Care and Long Term Results

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INTRODUCTION

Endonasal sinus surgery has been performed in our department for more than 40 years, and in recent years an endoscope has been used. In this paper, I discuss the postoperative care and long-term results of endoscopic endonasal sinus surgery for diffuse chronic sinusitis characterized by nasal polyposis.

Our surgical technique is performed under local anesthesia, and involves removal of the anterior and posterior ethmoidal cells via the middle meatus. We attempt to leave the mucosa of the ethmoidal sinus intact unless pathological mucosa exists. Next, sufficient communication between the ethmoid sinus and both the maxillary and frontal sinus is achieved under endoscopic observation. We attempt to heal the sinuses indirectly by achieving good drainage and ventilation.

SUBJECT AND METHOD

I compiled and analyzed 112 patients in whom 182 sides of diffuse chronic sinusitis were subjected to endoscopic endonasal ethmoidectomy with the creation of a large communication between the maxillary sinus and frontal sinus. These initial sinus surgical cases have been followed up postoperatively for periods ranging from 8 months to 5 years and 5 months. The age range was from 15 to 70 years, with a mean of 35.8 years.

The improvement rate of clinical symptoms by questionnaire, the improvement rate and the postoperative period required for cure of maxillary sinus lesion, and also the postoperative conditions of the ethmoid sinus, nasofrontal duct, fontanelle and maxillary sinus are analyzed.

RESULT AND DISCUSSION

Concerning the postoperative condition of the ethmoid sinus, good epithelization of the ethmoid sinus was observed in 136 sides, or 77.3% of the total. Some edema of the ethmoidal mucosa or small local polyps were seen in 27 sides, or 15.3%. Recurrence of polypoid mucosa in the ethmoid sinus was seen in 13 sides, or 7.4%. These patients had severe disease in the sinus preoperatively.

Concerning the postoperative findings for the nasofrontal duct, fully open cases numbered 103, or 73.6%, cases found to be open with edematous mucosa numbered 27, or 19.3%, and cases obstructed with a polyp were 10, or 7.1%.

Concerning the postoperative condition of the fontanelle after middle meatus antrostomy. The number of sides with a fully open fontanelle were 88, or 50%. While moderately open cases numbered 78, or 44.3%, and narrowed cases were 7, or 4%. Sides with a stenotic condition due to garanulation tissue or a polyp numbered 3, or 1.7%.

X-ray studies of the postoperative changes in the maxillary sinus were performed. There are four classifications of shadows in the maxillary sinus. Of 156 sides, 87 sides, or 57.1%, showed good improvement (improvement by at least two grades), 58 sides, or 37.2%, showed fair improvement (improvement by one grades), and 8 were unchanged.

The overall improvement rate in the objective endoscopic findings after surgery was 90 - 95%. Complete cure was not able to be obtained in 5 - 8% of the cases. They apparently require another treatment or surgical procedure.

I examined the postoperative period required for improvement in the maxillary sinus lesion. The subjects were 74 sides which could be checked regularly. The cure rate within 6 months was 58.1%, after 7 - 12 months it was 17.6% and at 1 to 2 years it was 19%. There were a few cases in which the lesions of the maxillary sinus finally became cured after more than 2 years postoperatively.

A questionnaire of various symptoms ranging from nasal obstruction to headache or heavy head was sent to the patients, who were asked to check one answer for each question before and after operation. For clinical symptoms, there are four classifications (-, +, ++, +++). The overall improvement was also graded into four classifications ranging from no nasal symptoms to severe nasal symptoms. Improvement by at least two grades is considered to be good improvement. Improvement by one grade is considered to be fair improvement.

Concerning nasal obstruction, good improvement was achieved in 79.8% of the cases and fair improvement in

19.3%. The improvement rates, calculated for good and fair improvement cases, for nasal discharge and post-nasal discharge were 92.4% and 90.9%, respectively, with 7.6% and 8.1% of the cases rated as unchanged. For headache or heavy head, 63.5% of the cases achieved good improvement, and 31.8% fair improvement. The overall improvement rate, including good and fair improvement, was 99.1% (good improvement 68.8%, and fair improvement 30.4%). None of the cases showed aggravation.

The subjective nasal symptoms improved in more than 90% of the patients. However, nasal discharge and post-nasal discharge persisted in a few cases. These 112 cases can be divided two groups. One is erythromycin administration group, the other is non administration group.

Recently I have tried to administer erythromycin after surgery. Erythromycin is now widely recognized as an effective drug (antibiotic) for diffuse panbronchiolitis. I have analyzed the data of long-term administration of low-dose erythromycin to 20 cases after endonasal sinusectomy.

The improvement rate of the clinical symptoms in the erythromycin administration group is compared with the untreated group. For overall improvement, excellent results can be obtained. (The good improvement rate was 95%) Also, concerning nasal discharge and postnasal discharge, the good improvement rate were 89.4% and 81.3%, respectively. These results indicate that long-term administration of low-dose erythromycin gives significantly better results than conventional endoscopic endonasal sinusectomy without erythromycin. (Fig.1)

The result of endoscopic endonasal sinus surgery is strongly dependent on the postoperative care. Postoperative care may include corrective surgery, treatment for the occurrence of adhesion, granulation tissue and polyps, and irrigation of the maxillary sinus. All these procedures can play an important role in obtaining good results. In addition, an antiallergy drug such as a steroidal nasal spray is effected for chronic sinusitis with allergy. Ordinary antibiotics must be administered for 2 weeks postoperatively. Furthermore, low-dose long-term administration of erythromycin for 3 - 6 months postoperatively is essential for treatment of severe diffuse chronic sinusitis.

Endoscopic endonasal sinus surgery enables a precise technique and facilitates the prevention of serious surgical complications, thereby improving the final

results. Also, long-term postoperative follow-up of at least 2 years, and appropriate postoperative treatment such as removal of polyps in sinuses are essential in surgical cases of chronic sinusitis in order to ensure good healing of the wound, and to obtain excellent results.

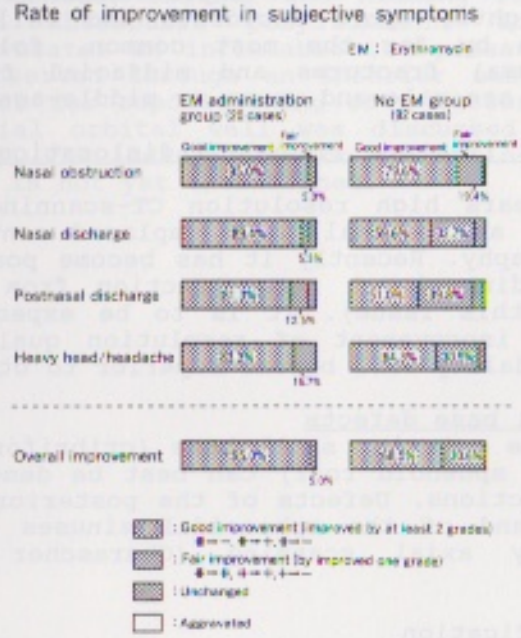

Fig.1 : Improvement rate of clinical symptoms by questionnaire

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Chairman's Introduction

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Facial bone fractures have a high incidence in all countries of the world. Their major causes are traffic accidents, fights, sport accidents and falls. Nasal fractures are by far the most common, followed by lateral (zygoma) fractures and midfacial fractures. Most patients are male and young or middle-aged.

3D imaging of fracture lines and dislocation of bone fragments

Since 5-10 years high resolution CT-scanning in two planes (axial and coronal) have replaced conventional X-ray photography. Recently it has become possible to compute a 3-dimensional reconstruction from the CT-data (Min - this issue). It is to be expected that with further improvement of resolution quality this diagnostic modality will become superior to others.

Anterior skull base defects

Lesions of the anterior skull base (cribriform plate, ethmoid roof, sphenoid roof) can best be demonstrated by coronal sections. Defects of the posterior wall of the frontal and of the sphenoidal sinuses are best visualized by axial scanning (Oberascher - this issue).

C.S.F. identification

According to the experience of the Salzburg Department the ß2-transferrin test is the best screening method for detection of cerebrospinal fluid leakage.
The natrium fluorescence test is more sensitive and helpful in assessing the location of the leak. Two ml of a freshly made natriumfluoride solution 5% in saline is injected intralumbarly. Immediately afterwards Merocel® sponges are placed in the upper part of the nasal cavity. The strips are removed the next morning and studied.

Reconstruction of midfacial skull base fractures. Approach

The incision is sometimes indicated by the skin lesions. The coronal incision gives a wide access from above, whereas the sublabial incision in combination with the degloving technique affords a superior approach from below. In orbital floor fractures an enlarged transconjunctival approach is advocated by Draf (this issue).

Fixation

Miniplates and microplates have proven to be of great help as compared to the old wiring technique. A disadvantage is that they have later to be removed. The newly developed IONOS bone cement has proven to be helpful for fixation of small fragments. Its longterm (side-)effects are not known however (Draf - this issue).
Reconstruction of the orbital floor is done by a 0.5 mm silastic sheet. Deitner and Hidding reported the use of an absorbable polydioxanone foils while Milewski advocates an inflatable low pressure balloon which is inserted through an inferior nasantrostoma. The technique for repositioning of a blowout fracture of the medial orbital wall was discussed by Uchida (this issue). The indications for correcting this type of fracture is not yet established.

Clinical Significance of 3-dimensional Computed Tomography (3-D CT) Performed in Maxillofacial Trauma

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INTRODUCTION

Radiologic evaluation of maxillofacial trauma is an important aspect in the evaluation of the acutely injured patient. They include simple roentgenograms, panorex projections, plain tomography, and computed tomography (CT). Recent developments in computed soft ware reconstruction now permit three-dimensional (3-D) CT reconstruction of complex anatomic parts. Since the bone has the highest attenuation coefficient, it is easy to distinguish and isolate from its soft tissue surroundings. Therefore, bony structures have proven easiest to reconstruct three-dimensionally. We have used GE 9800 Quick 3D Scanner at Seoul National University Hospital for the 20 months for the evaluation and surgical planning of facial fractures of 14 patients with complex injuries. This paper presents the advantages and current limitations of 3-D imaging in the head and neck area. We present 5 illustrative cases.

MATERIALS AND METHODS

From May 1989 to Dec. 1990 three dimensional computed tomography (3-D CT) was performed in 14 patients of complex maxillofacial trauma admitted to Seoul National University Hospital.

All patients were radiologically examined using GE 9800 Quick 3D Scanner. The following scanning parameters were used: 3 mm thick slices with 2.5 mm interval, 4-second scanning time at 100 mA and 120 kVp. The patients were placed in a supine position. Only axial images were used for 3-D reconstruction and 12 routine views were obtained in 3-D CT scan.

CLINICAL APPLICATIONS

Case 1. A 23-year-old man was transferred to the Seoul National University Hospital 1 day after an automobile accident that resulted in flattening of the left malar eminence. Physical examination and conventional computed tomography revealed step-like defect on the left lower orbital rim. Subconjunctival hemorrhage and trismus were found. Open reduction and internal fixation was performed. The CT scan of the injured face revealed fracture of lateral orbital wall and fractures of anterior and posterior walls of both maxillary sinuses. The 3-D CT scan showed mediposterior displacement, malar eminence depression and coronoid process fracture medial to the zygomatic arch (Fig. 1). The 3-D CT scan showed the direction and extent of fractures along with their spatial relationships. The operative findings confirmed both the physical findings and the roentgenographic assessment and these injuries were classified as left trimalar fracture and Le Fort II fracture.

Case 2. A 32-year-old man sustained severe facial injuries from pipe falling down and was transferred to the Seoul National University Hospital 1 day after injury. Epistaxis, open bite and distocclusion were found and right eye ball rupture was associated. The patient was managed by open reduction and internal fixation. The 3-D CT scan showed whole of the fracture line which can not be found on conventional computed tomography and left displacement of central fracture fragment. It was shown that the separation of fracture line in the right was wider than that in the left and the medial fragment was severely impacted on the left lateral portion of the maxilla (Fig. 2). In operative findings these injuries were classified as right trimalar and Le Fort II fracture.

Case 3. A 19-year-old woman was transferred 8 days after injury with severe mandibular and right tibia fractures. The injuries occurred after falling down from the third floor. Open wound was found in her chin. Open bite, cross bite and trismus were observed. This patient was treated by open reduction and internal fixation. The 3-D CT scan showed the exact extent of rotation and displacement of the mandibular fracture fragments. In this case it was possible to plan appropriate surgical procedures for the correct reduction of the fractures and spare operation time (Fig. 3).

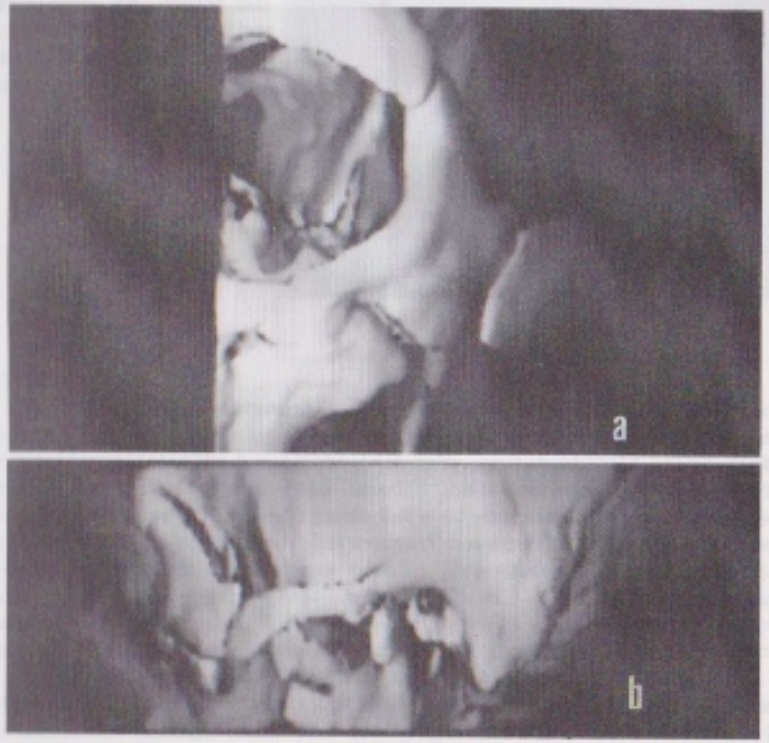


Fig 1. Three dimensional computed tomography of case 1. Fig 1-a taken from the front shows mediposterior displacement of fractured fragment of the left malar eminence. Fig 1-b taken from left lateral aspect shows medial displacement of fractured fragment of the zygomatic arch and coronoid fracture medial to the zygomatic arch.

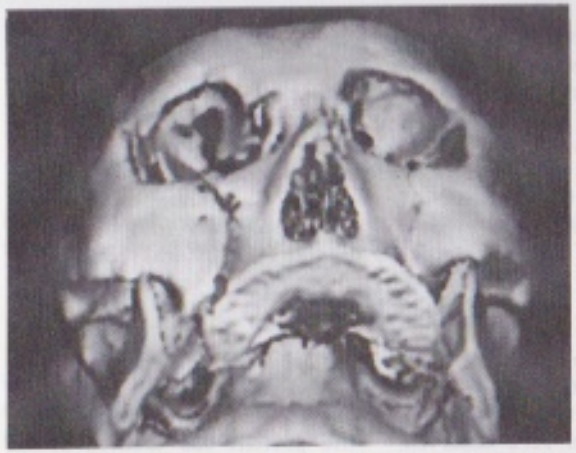


Fig 2. Three dimensional computed tomography of case 2 taken from below shows left displacement of the central fractured fragment. Fracture line in the right side is separated more widely than that in the left.

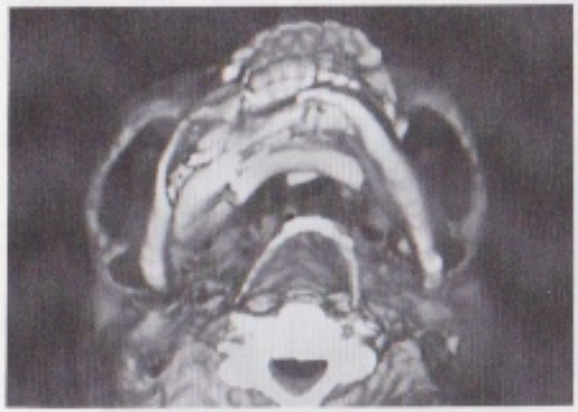


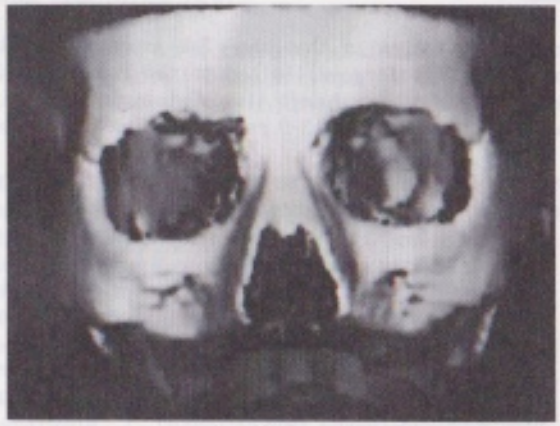
Fig 3. Three dimensional tomography of case 3 taken from below shows the extent of rotation and posterior displacement of the comminuted fractured fragments.

Case 4. A 22-year-old woman was transferred 3 days after injury with a chief complaint of blindness of the left eye. The injury occurred from falling down during bicycle riding. Total blindness and afferent pupillary defect of the left eye were observed. The CT scan showed fracture of the lateral wall of the orbit near the orbital apex. The 3-D CT scan revealed obvious medial rotation of fractured fragment of the lateral orbital wall (Fig. 4). The small fragment was removed and the patient had light perception after surgery.

Case 5. A 20-year-old man sustained facial injury following automobile accident and was transferred to the Seoul National University Hospital 1 day after injury. He complained of diplopia at upward gaze and enophthalmos was observed in the right eye. He had right orbital rim fracture and epidural hematoma. The CT scan showed the fracture of the right lateral orbital rim and epidural hematoma. The 3-D CT scan gave us more information about displacement of the small fragment (Fig. 5). The patient had open reduction and internal fixation.

Fig 4. Three dimensional computed tomography of case 4 taken from the front shows obvious medial rotation of fractured fragment of the lateral orbital wall. The fragment looks like small plate.

Fig 5. Three dimensional computed tomography of case 5 taken 45° obliquely from the right shows the exact site and inferomedial displacement of a small fragment.



DISCUSSION

The introduction of computed tomography revolutionizes the diagnostic radiology of facial fractures with improved visualization of the complex bony anatomy of the head and neck. However, in its normal axial format, viewing a series of CT scans is akin to looking at individual slices of bread, then trying to form a mental image of the whole loaf. To overcome this limitation of CT scans, attempts at computer reconstructions of the two-dimensional contiguous slices of the CT scan into a 3-D display have been made in the last several years. Three-dimensional CT reconstruction of complex anatomic parts provides a clinician with global image of the facial anatomy for preoperative or postoperative evaluation.

As these cases suggest, many of the spatial relationships not easily appreciated on conventional roentgenograms or conventional 2-D CT are easily conceptualized with the 3-D technique. Thus, not only the extent of the fracture sections but a suggestion of the mechanism of injury can be readily assessed. The 3-D display can be manipulated on the computer monitor and provide full volume 360° perspectives of the reconstruction, as

well as random sectioning in any desired plane. Fracture lines inside the skull, and the extent of the displacement and rotation can be assessed. The improved diagnostic capability, from the enhanced conceptualization of the structural derangements, reduces operating room time and decreases the likelihood of unforeseen difficulties during surgery. Other applications include preoperative evaluations of craniofacial anomalies, neoplastic diseases of the head and neck, and cervical spine injuries (Mattox et al, 1988).

The 3-D imaging does not provide new information that is not already stored in the digital data collected for conventional two-dimensional CT scans (Koltai, 1986). On 3-D imaging a thin bone can be seen as a pseudoforamina artefact according to increasing threshold value, and fracture lines without displacement can not be assessed. So conventional roentgenograms and tomograms of the facial region are helpful for correlation with 3-D cases.

Another limitation is that the 3-D process, probably due to thresholding limitations, is largely limited to the reconstruction of bony structures. Most cartilaginous and soft tissue structures are difficult to isolate from their environment for a 3-D reconstruction (Mattox et al, 1988).

Authors conclude that three-dimensional CT reconstruction is important for analysis and surgical planning of facial fractures.

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SURGICAL MANAGEMENT OF MIDFACIAL FRACTURES

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INTRODUCTION

90% of midfacial fractures include fractures of the nose and paranasal sinuses. This indicates the need of an ENT-surgeon for treatment of those lesions. According to Schroeder, Glanz and Kleinsasser (1982) facial fractures may be classified as nasal fractures only (55% of Fulda material N=960 1979 - 1990), midfacial fractures (45%) consisting of lateral (67%) and central ones (29%) and frontal sinus fractures (4%).

Frontal sinus wall fractures are in 34.6%, central midfacial fractures in 42.2% accompanied by skull base lesions, whereas in lateral midfacial fractures the skull base is injured in 3.6% only (Schröder et al. 1982).

SURGICAL TREATMENT: GENERAL ASPECTS

For surgical treatment the following general aspects have to be taken in acount: Diagnostics, interdisciplinary cooperation and timing if necessary, incisions and techniques of osteosynthesis. Timing is a very important point of surgical treatment. It demands large experience of all involved specialists. Only a few principles can be mentioned (see also Samii and Draf 1989): 1. Definitive complete primary care is superior. Interdisciplinary surgical cooperation in one session gives mostly better results than many single step operations. 2. Intracranial space-occupying lesions have to be treated first. 3. Reduction of extended facial fractures stops often severe bleeding. It has to be done before dural repair. 4. Decision about necessary tracheostomy should be made early. 5. Severe brain injury demands sometimes delay of surgical intervention. The surgical incision should provide not only for sufficient exposure, but also for hidden scars as much as possible. For approach can be used: 1.Soft tissue lacerations, 2. Sublabial incision, 3. Degloving technique, 4. Enlarged transconjunctival incision, 5. Coronal incision. Fractured parts of the facial sceleton need osteosynthesis, if they are dislocated to a major degree, mostly for functional and often for esthetic restoration. Aims are: Minimal surgical trauma, avoidance of secondary intervention and stable contouring. Possible techniques are: resorbable sutures, wire ligations, miniplates, microplates and the new IONOS bone cement.

Since about 1 year we test in a clinical study the IONOS bone cement for fixation of smaller bone fragments. It has the advantage of connection with bone in a chemical way very strongly similar to an excellent glue, but getting hard like a bone. One is able to fix together two or more pieces of bone to one part. This

bone cement can be modeled easily with a diamond burr. It seems like it can replace the other types of osteosynthesis under many circumstances.

SPECIFIC ASPECTS

Some specific aspects regarding treatment of facial fractures should be mentioned: 1. In frontal sinus wall fractures we look very carefull, if there is a lesion also of the posterior wall. If the fragments are dislocated, we tend in most of the patients to revision to see if there is a dural lesion or not. Otherwise life threatening complications may occur. 2. In cases of abducent nerve pareses we are conservative. As long as the nerve is intact, the function recurs within one or two months. 3. A fracture of the sphenoidal wall of the internal carotid artery with dislocation of fragments needs revision. We saw two patients with fragments penetrating the wall of the internal carotid artery. The small pieces of bone may necrotize and lead to bleeding or the lesion ends up in a carotid-cavernous sinus fistula. We removed the fragments and closed the leakage with fascia lata or preserved fascia putting it between the wall of the carotid artery and the bony surrounding using fibrin glue. 4. Sometimes midfacial fractures are combined with lesions of the lacrimal drainage system, either the canaliculi or the nasolacrimal duct. If we find lacerations of the lids we have to look with a microscope for lesions of the canaliculi. We intubate injured canaliculi with our modified atraumatic pigtail probe and suture them microscopically. In cases of postsaccal stenoses, which may happen weeks or months after trauma, the microsurgical endonasal dacryocystorhinostomy is the easiest way to release the patient from his problem.

SUMMARY

A brief overview has been given about types, diagnostics and therapy of midfacial fractures. The ENT-surgeon should play an important and active role in the treatment. In extended cases interdisciplinary cooperation will give better results.

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ORBITAL WALL FRACTURES

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INTRODUCTION

About fifty to sixty percent of the orbital wall also constitutes the wall of the paranasal sinuses. This fact means that orbital wall fractures simultaneously entail damage to the paranasal sinuses at same time. The purpose of this paper is to describe the treatment of blow-out fractures via the sinuses.

STATISTICAL DATA

Forty-six patients were treated during past 10 years in our ENT department and/or affiliated hospitals. The 42 patients consisted of 38 males and 8 females. The age distribution and number of patients are shown in Fig. 1. The causes of injury was traffic accidents in 11 cases, fighting in 10 cases, and accidental trauma and falls. The site of injury was the medial wall of the orbit in 18 cases, the orbital floor in 27 cases and simultaneous injury of the medial wall and orbital floor or crush injury of the root of the nose in seven cases. The severity of orbital wall fracture is related to the site, direction, strength and nature of the applied force, the thickness of the bone, and other factors. In this con-nection, the mean values for the thinnest region of the orbital walls were 0.56 mm for the roof, 0.26 mm for the medial wall, 0.56 mm for the floor and 1.39 mm for the lateral wall.

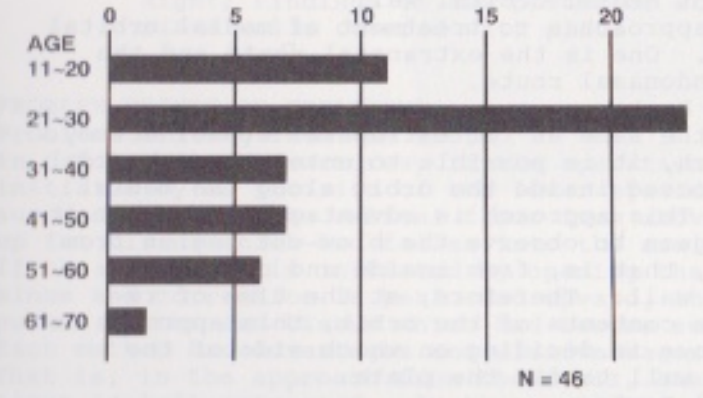

Fig. 1 Age distribution

APPROACH FOR REPOSITIONING OF FRACTURES

1. Orbital Floor Fracture

In accordance with the method of Caldwell-Luc, the canine fossa was opened, the mucous membrane was conserved whenever possible, loose bone fragments were removed, and protruding fat tissue was gradually compressed and replaced inside the orbit. Then a silastic plate with a thickness of 0.5 mm was applied, and a balloon catheter was inflated over the plate to fix the fat tissue for at least three weeks. In some cases, silastic blocks were used as supporting pillars in place of a balloon (Fig. 2). These silastic blocks were removed after about one month.

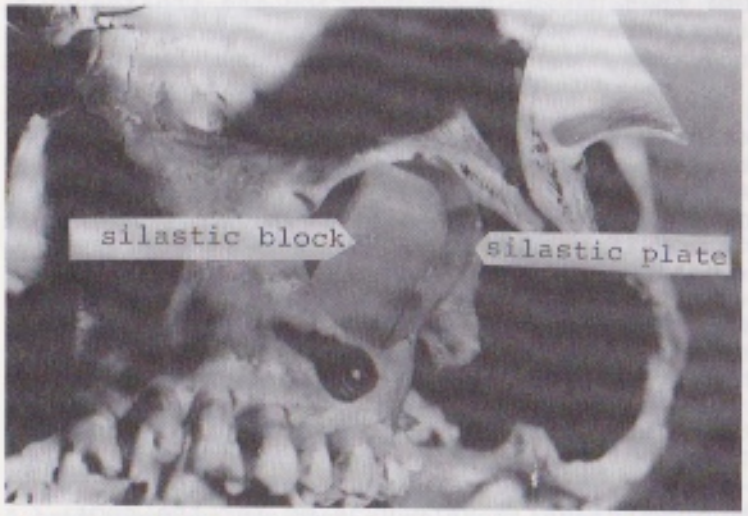

Fig. 2 Repair of the orbital floor fracture using a silastic plate and silastic blocks

2. Fractures of Medial Orbital Wall

There are two approaches to treatment of medial orbital wall fractures. One is the extranasal route and the other is the endonasal route.

2-1. External Route

This route is the same as for extranasal ethmoidectomy. In this approach, it is possible to enter the ethmoidal sinus or to proceed inside the orbit along the medial orbital wall. This approach is advantageous in that it enable the surgeon to observe the blow-out region from two directions, that is, from inside and outside the medial orbital wall. Therefore, at the time of repositioning the contents of the orbit, this approach is also advantageous in deciding on which side of the medial orbital wall to fix the plate.

2-2. Endonasal Route

This method can also be said to be an application of endonasal ethmoidectomy. In this route, endoscopes are very useful. While observing through an endoscope, small bone fragments are removed, large bone fragments are repaired, and fat tissue is returned inside the orbit. Even when the ethmoidal bulla looks normal, the posterior region behind the ground lamella of the middle turbinate has been destroyed in most cases. If the fracture is seen to extend infralaterally toward the roof of the maxillary sinus, there are limitations to the value of this endonasal approach. After repositioning, it is recommended that the contents of the orbit be supported with a silastic plate for 3-4 weeks, as in the external approach. If local anesthesia is employed, the surgeon can request the patient to perform eye movement and check the result of the operation (Fig. 3).

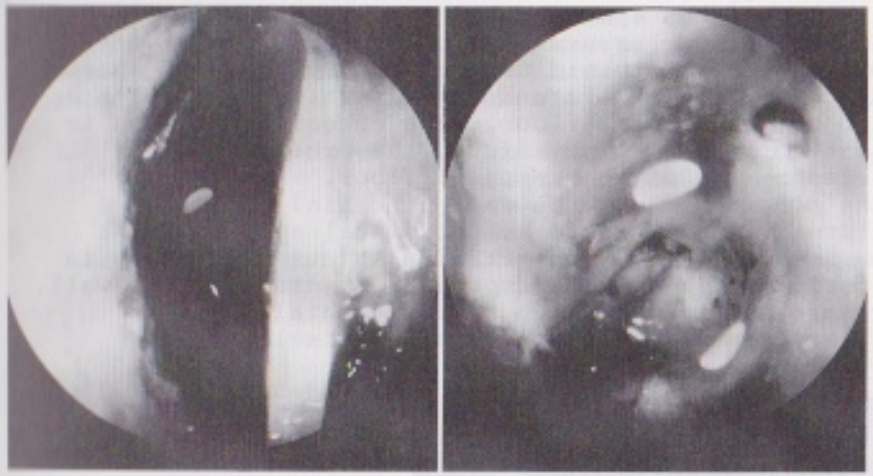

Fig. 3 Repair of the medial blow-out fracture
Left; Middle meatus fixed with silastic plate
Right; Findings of the posterior ethmoidal sinus walls covered with plate

PROBLEM POINTS OF TREATMENT

Problems Arising from the Route

In orbital floor fractures, if the operation is initiated by an incision of the lower eyelid, the surgeon observes the orbital floor from above and pulls up fat tissue which had fallen into the maxillary sinus. If the operation is initiated by opening the maxillary sinus and correction is performed upward, the surgeon pushes up the fat tissue which had become suspended. Each method has advantages and disadvantages. That is, in the approach from the orbit, the maxillary sinus is left untreated. In the maxillary sinus approach, on the other hand, it is difficult to insert

supporting materials into the orbit. In this maxillary sinus approach, a balloon or silastic blocks are often inserted, and these are removed after a certain period of time. If the surgeon is reluctant to insert and leave a supporting material in the orbit, the maxillary sinus approach may be unavoidable.
In the treatment of either orbital floor fractures or medial orbital wall fractures, two routes are available. In some cases it is acceptable to employ two routes the same time. Especially in the case of an injury extending from the orbital floor to the medial wall, we should not limit ourselves to one route. This is because a sufficient surgical field and reliable repositioning and fixation are necessary.
Blow-out Fractures without Visual Symptoms
There are cases which show clear damage to the orbital wall on image diagnosis, but there is no double vision, retraction of the eye or other symptoms. Moreover, some cases show disappearance of diplopia as a result of a good response to steroid treatment. These cases should be discussed from the standpoint of rhinology. With regard to the orbital floor, if a chronic infection is present in the maxillary sinus, the orbit may be infected by way of the ruptured floor.
On the other hand, in the case of medial orbital fractures, even if there are no visual symptoms, fat tissue may remain in the ethmoidal sinus if surgery is not performed (Fig. 4). Around the medial orbital wall, there are natural openings to the frontal sinus, maxillary sinus and ethmoidal sinus itself.

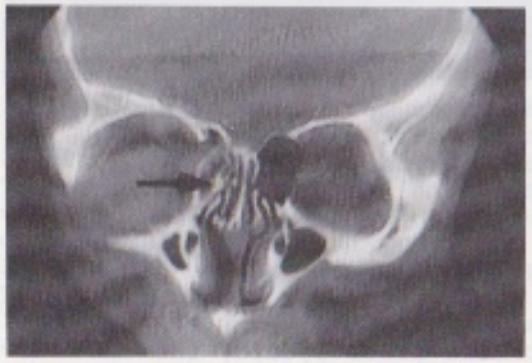

Fig. 4 A case of the medial blow-out fracture without symptom

If fracture and compression of this region are left untreated, the natural openings may be affected by the lesion and undergo stenosis or obstruction. Therefore, even if there is no manifesta-tion of symptoms soon after injury, we cannot rule out the possibility that,

in the future, as the wound becomes a scar, cyst formation or chronic infection may occur due to obstruction of the natural openings of these sinuses.
From this point of view, although the primary objective of surgery is to try to reposition the orbital contents which have been displaced, a second objective is to clean the injured ethmoidal sinus and restore patency to the natural openings of the sinuses. These objectives are the same regardless of the surgical approach employed.

CONCLUSION
After injuries to both the orbital floor and medial orbital wall, the objective of treatment is to restore the structure and function of the visual organ and paranasal sinuses. We should select an appropriate route of approach which can achieve both objectives. If no such route is available, there are no problems in select-ing two routes at the same time, and we believe we should not adhere to only one route.

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Summary of the Fireside Conferences

FIRESIDE CONFERENCE 1 AUTONOMIC NERVE CONTROL OF THE NASAL MUCOSA

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During the last decade morphological, biochemical and physiological studies in man and various experimental animals have provided increased knowledge on nasal physiology and pathophysiology. The introduction of immunohistochemistry and immunoassays for identification and localiza-tion of various mediators have provided remarkable tools for studying their formation, storage, release and function within the autonomic nervous system. Technical problems and species differences may account for conflicting data reported in various experimental studies indicating that data shold be interpreted with caution. During the conference following topics were discussed and commented.

Autonomic sensory and motor innervation of the nasal mucosa

Autonomic sensory and motor nerves are abundant in the nasal mucosa. In addition to the classical transmitters (CT) present in adrenergic and cholinergic nerves, a third division called the nonadrenergic, noncholin-ergic nervous system (NANC) is now well accepted. Neuropeptides are the most documented transmitter candidates for the NANC-innervation. By means of immunohisto-chemistry, several biologically active poly-peptides such as substance P (SP), neurokinin A (NKA) and calcitonin gene related peptide (CGRP) have been demonstrated in a subpopulation of trigeminal nasal afferents presumably belonging to the C-fibre group (fig1). These C-fiber afferents are specifically activated by capsaicin. (see Lundblad 1984, Stjärne 1991.)

Postganglionic sympathetic neurons located in the superior cervical sympathetic ganglion contain in addition to noradrenaline (NA), neuropeptide Y (NPY), somatostatine (SOM) and opiates. They innervate mainly arteries, arterio-venous shunts, venous sinusoids and venules. Parasympathetic fibres containing acetycholine (ACh), vasoactive intestinal polypeptide (VIP) and peptide histidine isoleucine (PHI) innervate mainly exocrine glands and sparsly resistance and capacitance vessels of the nasal mucosa. In some species such as the pig, parasymphathetic fibres may also contain NPY.(see Lacroix 1989)

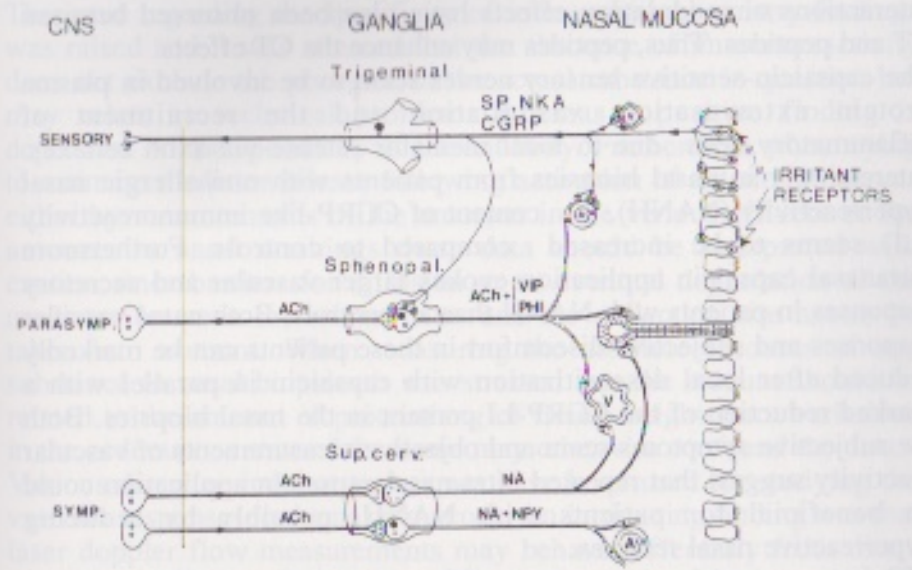

Fig 1. From Lundblad

The functional significance of both CT and neuropeptides in the nasal mucosa has been studied in various in vivo and in vitro models. In pentobarbital anaesthetised pigs, parallel recordings of nasal arterial blood flow (BF), capacitance vessels function (i.e. nasal mucosal volume V) and superficial movement of blood cells (via a laser Doppler flowmeter, LDF) have been studied. The vascular responses to sympathetic or sensory nervous stimulation can be recorded in parallel to the overflow of both CT and NANC agents in the nasal venous outflow. Generally high frequencies of stimulation are necessary to evoke peptide release. However, in the sympathetic and sensory nerves, a single impulse evokes presumable peptide mediated responses. In contrast to the release of CT, peptide release cannot be maintained over prolonged stimulation periods due to a restricted resupply which is dependant on axonal transport. Most of the remaining vascular responses to nerve stimulation observed in spite of pharmacological blokage of the CT receptors can be mimicked by local intra arterial infusion of the colocalised peptide. Generally speaking the neuropeptide response is characterized by beeing slow in onset and long lasting, whereas the CT responses are rapid and short lasting.

Denervation induced supersensitivity as demonstrated for CT has also been shown for peptide responses suggesting modulation of receptor function under physiological conditions. The occurence of synergistic interactions or modulatory effects have also been observed between CT and peptides. Thus, peptides may enhance the CT effects.
The capsaicin-sensitive sensory nerves seem to be involved in plasma protein extravasation, vasodilation and the recruitment of inflammatory cells due to local mediator release via axon reflexes. Interestingly in nasal biopsies from patients with non-allergic nasal hyperreactivity (NANH), the content of CGRP-like immunoreactivity (LI) seems to be increased compared to controls. Furthermore intranasal capsaicin application evokes larger vascular and secretory responses in patients with NANH than in controls. Both nasal vascular responses and subjective discomfort in these patients can be markedly reduced after local desensitization with capsaicin in parallel with a marked reduction of the CGRP-LI content in the nasal biopsies. Both the subjective symptoms score and objective measurements of vascular reactivity suggest that repeated intra-nasal capsaicin application could be beneficial for patients with NANH, possibly by reducing hyperreactive nasal reflexes.
Efficient antagonists to neuropeptide receptors are still lacking in order to clarify their implication in the development of pathophysiological processes. However, interference at release sites of sensory neuropeptides by repeated local capsaicin analogue application may represent a new therapeutic approach for the treatment of chronic and nonspecific hyperreactivity disorders of the nose.

Receptor function - Pathopysiological importance in disease.

Using receptor binding techniques Kubo et al. (1989) when studying biopsies from the nasal mucosa in patients suffering from perennial nasal allergy demonstrated reduced concentrations of α-1 and β-adrenergic receptors and increased muscarinic receptor concentrations. Furthermore when the enzymatic activities of tyrosine hydroxylase (TH) and dopamine β hydroxylase (DBH) were studied, enhanced activities of TH and reduced activities of DBH were found. This indicates that repeated sympathetic activity results in a depletion of DBH in the sympathetic nerve terminal with a subsequent disturbed NA synthesis. The presence of anti β receptor antibodies has also been postulated from studies demonstrating a β receptor binding inhibitory IgG component in the sera of 12 out och 60 patients suffering from perennial nasal allergy. This finding was also observed in sera from 5 out of 50 patients with pollinosis. It might be speculated whether this may affect β adrenergic receptor function and thus be a factor of

importance in the pathophysiology of nasal hyperreactivity

Discussion.

The issue regarding the specificity of immunohistochemistry findings was raised and it was stressed that the abscence of immunoreactivity does not exclude the presence of the actual substance in question but may relate to technical problems whereas a positive finding is dependant on the specificity of the antibody. Furthermore when trying to estimate mediator release following activation of autonomic nerves either by measurements of the amounts in the venous effluent or the amounts in nasal washings these data should be interpreted with caution since barriers for diffusion or an eventual degradation of the mediator between the release site and the collection site has to be taken into account. When measuring the absolute amounts of any substance in nasal biopsies it was stressed that the amount should be related to the amount of protein/ mg of tissue weight since variations in the oedematous state of the tissue may otherwise confound the data.
Various direct or indirect techniques have been used for studying the vascular responses in the nasal mucosa. An intrigueing finding was that laser doppler flow measurements may behave differently from direct measurements of total blood flow. Thus a decrease of the laser doppler signal indicating a decrease in flow velocity may occur at the same time as an increase in total blood flow is recorded. This is probably related to the complex vascular anatomy of the nasal mucosa with the presence of arterio-venous shunt vessels and a superficial capillary plexus and a deeper periglandular capillary network. The laser doppler probably records from a limited superficial part of the nasal vascular bed. A redistribution of blood from this area to the deeper areas following increased glandular activity and blood flow or increased flow through arterio-venous shunt vessels could explain these discrepancies.
Furthermore these data suggests that any indirect technique used for the estimation of blood flow changes should be evaluated in relation to direct flow measurements.
The physiological importance of the coexistence between the classical transmitter (CT) and neuropeptides in the efferent autonomic responses was discussed. It was stressed that the lack of effective peptide antagonists makes it difficult to analyze their relative importance in physiological and pathophysilogical processes in the nasal mucosa. Experimental evidence demonstrating a corelease of the CT and respective neuropeptide as well as vascular responses following autonomic nervous activation in spite of inhibition of the responses induced by the CT suggests a physiological role for the neuropeptides in the nervous responses.

The interpretation of data regarding receptor densities and receptor bindings of adrenergic and cholinergic agonist obtained from in vitro studies were discussed in relation to results obtained from pharmacological in vivo experiments. The demonstration of β receptors in the nasal mucosa have not been found to relate to any major vascular effects in the nasal vascular bed following autonomic nervous activation apart from a slight increase in arterial blood flow. No effects on blood volume changes have been demonstrated. This would indicate that β receptors presumably are activated by circulating catecholamines. Furthermore pharmacological treatment with β-blocking agents has mainly been associated with side effects of hypersecretion rather than nasal blockage. The increased number of cholinergic receptors in patients with nasal hyperreactivity has been clearly demonstrated. However, weather this is due to an increased number of glandular elements in the nasal mucosa or an increased number of receptors on the glandular elements is not known. However it has been demonstrated that the secretory response correlates to the density of cholinergic receptors and the density and nasal blockage to the density of α1 receptors.
The question regarding nose drop abuse was raised. No one could give any substantial evidence weather this condition is due to an interference with receptor modulation or down regulation of α–receptor activity. The conference provided an interesting forum for discussion on the physiology of the nasal mucosa and pathophysiological aspects on hyperreactive disorders of the nose. Furthermore, many interesting new ideas were brought to mind hopefully resulting in further well designed experiments. The results of which will hopefully provide data for another conference.

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Proceedings from the fireside conference.

M. Tos [1] (Chairman), Y. Sasaki [2] (Co-chairman), M. Ohnishi [3], P. Larsen [1] and A.B. Drake-Lee [4].

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In the literature there is great disagreement on the pathogenesis on nasal polyps. Several theories on polyp formation have been described, but nearly all conclusions have been deduced from the histopathological studies on the fully developed polyps. Nobody has histologically demonstrated how nasal polyps formation take place. The goal of this fireside conference is to discuss some of the pathogenetic theories hopefully to put some more light on polyp formation.

The first panellist dr Ohnishi put forward the theory that vascular congestion with obstruction of the return flow of tissue fluid through the thin stalk is responsible for the formation and volume of the polyp. He measured blood flow by hydroxygen clearance method in 27 patients with chronic polypoid pansinusitis. Significantly lower blood flow was found in nasal polyps and in polypoid tissue from the middle turbinate and middle meatus than in the non polypous mucosa of the middle turbinate, inferior turbinate, and septum from the same patients. Between the nasal polyps and polypoid middle turbinate or middle meatus mucosa no significant difference of blood flow was found. Dr. Ohnishi concluded, that poor vascularity in the nasal mucosa coincided with areas of occurrence of nasal polyps, and that poor vascularization of the mucosa is a factor for development of nasal polyps.
The second panellist dr. Larsen tried to bring some more support for the "epithelial rupture theory" on nasal polyp formation brought forward in 1977 by Tos (6). According to this theory rupture or necrosis of nasal epithelium may occur because of oedema and increased tissue pressure in infection or allergy combined with blockage of the air flow in the middle and superior meatus, resulting in prolapse of the fibrous tissue from the lamina propria through the epithelial rupture. Protrusion of the fibrous tissue will be gradually epithelialized and a small polyp can be formed. During epithelialization and continuous

growth of the polyp, especially because of gravity phenomenon and vascular congestion of the return flow, the polyp will grow and newformed glands are formed in the polyp. These glands have previously been demonstrated in all polyps (7). By the epithelial rupture theory the presense of the pathological newformed glands in nasal polyps can be explained, but the very first stage of the epithelial rupture or defect have never been demonstrated histologically in the nose, in particular due to lack of suitable material in the very first stage of polyp formation. Dr. Larsen studied 65 Wistar rats with long-term tubal occlusion and found signs of polyp formation or fully developed polyps in 14 middle ears (22 %). It was established that the first stage of polyp formation in middle ear mucosa include epithelial rupture, proliferation of fibrous tissue through the epithelial defect and epithelialization of protruded fibrous tissue. By further proliferation and migration the epithelial cells from the surrounding epithelium, full epithelial covering of the polyp will occur. Incipient epithelialization of the new polyps were seen in 4 middle ears (3), in three cases a partial epithelialization was found and in one case nearly total epithelialization had taken place except in the apical part. Fully epithelialized polyps were seen in 7 middle ears. Dr. Larsen demonstrated that epithelial rupture is a possible model in the middle ear, but the question still remains whether this model is actual in the nasal and sinus mucosa.

The third panellist dr. Drake-Lee did not speak about the pathogenesis, but more about the etiology and treatment of nasal polyps. He emphazised that etiology of nasal polyps is uncertain in the majority of cases, however, there are few known associated diseases with development of nasal polyps which include cystic fibrosis and primary ciliary dyskynesia. In his opinion the polyps in adults are heterogeneous collections of diseases since some patients have more severe recurrences and this is associated with aspirin hypersensitivity, asthma and at an early age of onset. Dr. Drake-Lee pointed out that the most current discussed surgical treatment of nasal polyps, the endoscopic nasal surgery has until now in prospective trials not documented it's superiority to other alternative methods of treatment, like simple nasal polypectomy, but it is documented that ethmoidectomy is associated with increase of complications, especially in cases where endoscopic nasal surgery is used in unqualified hands. In his opinion the routine surgical treatment of choice should be simple nasal polypectomy until the adequate trials should document the superiority of ethmoidectomy. The treatment was not further discussed at the fireside conference.

Several pathogenetic theories have been explained by the chairman and discussed among the panellists and the audience. The old "adenoma theory" (1) based on findings of newformed glands and the "fibroma theory" based on absence of glands in the polyp stroma in the so called fibrotic polyps have been rejected in the past century. So was the "chronic ethmoiditis theory" (8) after which a necrotising ethmoiditis leads to necrosis of bony septa of the ethmoidal cells and to a myxoematous focus projecting from the ethmoid into the nose in the form of a polyp. None of the panellists or the audience believed that the necrotic ethmoiditis today could be a cause of nasal polyp formation.

The ethmoiditis theory brought forward the question of origination of nasal polyps. Some surgeons believe that the primary cause of polyp formation may be an ethmoiditis causing an eodematous and polypous mucosa which can be projected through the ostia as a polyp, but in my opinion it is hard to believe that an expanding polyp filling all the ethmoidal cell can just pass the ostium and show itself as a nasal polyp. I believe that the primary cause and the most common places of nasal polyp formation are the middle and upper meatus, especially nasal mucosa of the ostiomeatal complex. Our study about origination of nasal polyps on six cadavers shows that all polyps of these specimens originated from the nasal mucosa. Recent studies by Stammberger (5) demonstrated that nasal mucosa was the origination of nasal polyps in 80 % of cases undergone functional and nasal endoscopic ethmoidectomy.
Hajek (2) believed that the formation of polyps starts in the nasal mucosa with accumulation of effusion which is pressed caudally. A vascular stalk would form and the vascular congestion would increase the volume of the polyp. Hajek's pathogenesis (2) still have many supporters because it fits well in the modern theories of eodema formation after infection, allergy, mast cell degranulation, vasomotor denervation, gland denervation, histamine release, vascular congestion and others which all together claim that some pathological stimulus will increase vascular permeability, create oedema of the nasal mucosa and polyp formation (4). The problem of all these theories which are based on diffuse oedema is that they cannot explain why the polyps form in one particular part of the nasal mucosa but never in another. General causes like infection, allergy, aspirin idiosyncrasy, mast cell degranulation and so on are supposed to create oedema of all nasal mucosa, not only in particular areas. The theory which is based on prolapse or simple protrusion of an oedematous mucosa does not fit into the findings of the distribution of pathological glands in the nasal polyps. Tos and Mogensen (7) have shown that the glands in nasal polyps are tubulous, having a special shape and distribution which definitely prove that they must be formed in the polyp during the polyp formation. That means that these glands are not originated from the

nasal mucosa and are not pushed by oedema into the polyp. These glands do not resemble nasal mucuos glands. The nasal glands are tubulo-acinous, they are arranged in two layers in nasal mucosa, their density is high (7.1 glands per mm^2). Such glands should be found in the nasal polyp, if the polyp is a simple prolapse of an oedematous nasal mucosa as stated by the majority of the theories. Such tubulo-acinous nasal glands were not found in nasal polyps.

In discussing the present theory of nasal vascular congestion presented by dr. Ohnishi two factors can be pointed out: On one hand obstruction of the return flow through the polyp stalk is the reasonable explanation for growth of the polyp and further increase of the polyp size may have this mechanism, but as soon we are talking about the stalk of the polyp, then the polyp is allready established, and is not at it's initial fase of formation. Vascular congestion can be the explanation for further growth of the polyp and/or for recurrence of the polyp, but not for the initial formation. Another part of dr. Ohnishi's theory is based on his excellent measurements of nasal flow in different parts of the nasal mucosa and should explain the initial fase of polyp formation, which means that anaemia of the mucosa should be the cause of oedema and polyp formation. This original thinking is in contrast to all other theories which claim that increased flow in the mucosa leads to exsudate or transudate within the mucosa and oedema. Increased vascularity of nasal mucosa is in fact documented histologically in all studies of an inflammated or infected non polypous nasal mucosa. In the discussion of dr. Ohnishi's theory the wellknown cause-consequence problem occurs. I believe that diminished vascularization of a polyp and of polypoid and oedematous tissue is a logic consequence of oedema, but can hardly be the cause of oedema.

Dr. Stierna from Stockholm showed experiments on rabbits with infected sinus mucosa. He clearly demonstrated that epithelial defect and epithelial necrosis is common in experimental sinusitis, and that prolapse of fibrous tissue which occurs as a consequence of infection will be covered by a newformed epithelium. In fact exactly the same process which was suggested by Tos in 1977 with the epithelial rupture theory of nasal polyp formation (1) was demonstrated histologically.

Finally dr. Stammberger from Graz showed very interesting pictures of attachments and origination of nasal polyps which in his opinion in the vast majority of patients take place in the middle meatus of the nasal mucosa around the ostio-meatal complex (5).

The conclusion of the fireside conference was that there are several possibilities for polyp formation; the epithelial rupture theory is only one of them. The origination of polyps is the nasal mucosa, most often around the ostio-meatal complex. We still do not know which factors are responsible for the oedematous mucosa becoming a polyp stalk. Much more research have to be done to clarify this and many other problems.

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Chairperson : In-Yong Park, M.D. (Korea).
Co-Chairperson : Soontorn Antarasena, M.D. (Thailand).
Speakers : Haskins Kashima, M.D. (U.S.A.).
Yasuo Hattori, M.D. (Japan).

Introduction : By Chairperson.
The purpose of this conference is to review the present pool of knowledge concerning nasal papilloma. It is obvious that all of us are interested in nasal papillomas. Hopefully a highly specialized yet practical free discussion will follow. The contributors to this conference were chosen because it is hoped that their areas of investigation will shed a new light on this subject of nasal papillomas. This will surely enhance collaboration between speakers from different countries and different working disciplines.

Dr. Antarasena presented the general view of NP including the biological characteristics, nomenclature, incidence, and recurrence rate.

Dr. Kashima presented the title of "Human Papilloma Virus and Sino-Nasal Papillomata and Squamous Carcinoma".

The diagnostic and prognostic relevance of human papilloma virus(HPV) types 6, 11, 16 and 18 in squamous papilloma, inverted papilloma and squamous carcinoma of the sinonasal epithelium was examined using the polymerase chain reaction (PCR)technique. Four of 22(18%) squamous papilloma, seven of 25(28%)inverted papilloma and one of 24(4%)squamous carcinoma were positive for HPV when examined utilizing PCR application technique.

HPV 6 was present in 5 specimens (3 squamous and 2 inverted papilloma), HPV 11 was present in 6 specimens(1 squamous and 5 inverted papilloma) and HPV 18 was present in 1 of 24 squamous carcinomas. HPV 16 was not identified in any specimen. The proportion of tissue samples showing HPV presence, and the association of HPV types 6 and 11 in benign lesions and HPV 16 and 18 with malignant lesions, are both in accord with findings from prior investigations.

Two major questions regarding nasal papilloma are the probability for lesion recurrence after surgical excision and the risk for malignant transformation. There is no unanimity of opinion regarding the prognostic value of histopathologic dysplasia to forecast these outcomes. HPV is etiologically related to a subset of sino-nasal papillomata and squamous carcinoma, and those with benign and malignant clinical course are separable on basis of HPV type. Because of the paucity of these nasal lesions, a multi-institutional prospective collaborative study is the ideal way to address these questions.

Dr. Hattori presented the title of the "Ultrafine Structure of the Nasal Papillomas".

The morphological characteristics of nasal papilloma resemble those in maxillary cancer and include the following: 1) squamous metaplasia, 2) gaps in the basal lamina, 3) infiltration of cytoplasmic processes of tumor cells and tumor cells into the stroma through the gaps in the basal lamina, 4) mitotic figures of some differentiated cells, 5) decrease in cells arrayed adjacent to the basement membrane, and 6) an increase and an irregularity in hemidesmosomes. For this reason, it is suggested that morphologically nasal papillomas are located between normal epithelial tissues and cancer tissues, and that nasal papillomas can be said to be a precancerous condition in a broad sense.

Question I : Is the papilloma virus present only in the papilloma cells or do they also occur in neighboring normal cells?

Response : The human papillomavirus(HPV) DNA is present in both the papilloma lesion as well as in normal cells. Biopsies of normal epithelium obtained from patients with recurrent respiratory papilloma, have been demonstrated to have HPV-DNA. Similar findings have also been reported from the genital tract epithelium in patients with condyloma. Demonstration of an HPV in normal and abnormal cells is documented by the technique of in-situ hybridization.

Question II : Failure to identify virus in papilloma and related lesions.

Response : Identification of virus depends on verifying the presence of a specific nucleic acid sequence, characteristic for a particular virus type. The technique of molecular hybridization uses a probe of known composition and having

specifity for a particular virus type of subtype. Failure to identify a particular virus type depends on the presence of the virus, in sufficient copy numbers and the use of the appropriate probe with sensitivity and specificity for that virus type. Lesions in the upper aerodigestive tract, in general have lower copy numbers than those in the genital tract. The technique of polymerase chain reaction has made possible the amplification of a small quantity of DNA so that it is more readily demonstrated using any of the variety of molecular biological techniques.

Question III: What is the criteria for probe selection?

Response: The probes have high specificity or broad specificity. The latter would be used for screening purposes and the former for identifying a highly specific identification of a virus type in association with a particular histologic or other clinical lesion. The probes can be selected on basis of sensitivity and specificity depending on the objective for the study.

Question IV: Comment on the transmission of genital tract HPV to the upper aerodigestive tract.

Response: The papillomatous lesions of the upper aerodigestive tract, laryngeal as well as the nasal have been predominantly from HPV type 6,11,16 and 18. The clinical expression of respiratory disorders follow the pattern previously described for the genital tract lesions in that type 6 and 11 associated with clinical and histologically benign lesions whereas HPV types 16 and 18 have been identified in lesions with higher risk for malignant transformation. In the case of the nasal lesions, as already discussed, the case numbers have been small but the pattern appears to follow those already established and described in the laryngeal lesions. It is presently thought that the primary mode of transmission of HPV infection in from an infected birth canal to the susceptible upper aerodigestive tract epithelium, be it larynx or nose. In the case of lesions with clinical expression in childhood, this manner of transmission would appear to be a reasonable explanation. For lesions of the larynx or of the nose whose clinical expression appears only after adulthood and sometimes into the fifth and sixth decades, a long latent virus infection is one possibility and the second is the acquiring of the viral infection during adult life, presumably through intimate exposure. The epidemiological evidence for the latter is sparse. Question V: Comment on the use of anti-viral agents, particularly interferon.

Response : The question of efficacy of interferon in papilloma disorders has been under active investigation by a number of medical centers. In the United States two major randomized studies were performed in the early 1980s. In one study using interferon obtained from pooled blood bank material, the clinical benefit of interferon was regarded to be short-lived and discontinuation of medication was accompanied by relapse in a high proportion of cases. In the second study purified interferons were obtained from cultured lymphoblastoid cells. During the corss-over study 17% of patients achieved complete remisssion and a third of the patients achieved partial remission. This initial study was a six month cross-over study only. Recently the experience of the patients from this randomized cross-over and who elected to remain on long-term interferon was reported. Just under 40% of the patients achieved complete remission and a similar number achieved partial remission. These unexpectedly high rates of favorable response to the interferon wewe most gratifying. Regrettably the precise natural history of this disorder, recurrent respiratory papillomatosis, is not known. We are presently planning to perform a comparative study to contrast the efficany of several interferon preparations. The primary difference between the two randomized controlled studies that were performed in the early 1980s is that the dose rates were significantly different and that sufficiently high doses were necessary to achieve clinical response. Given the similar viral etiology for the nasal and inverted papillomas, and the exceedingly difficult control rate using surgical therapy only, the search for an effective adjuvant goes on and at present, interferon amy be the leading candidate to answer this need.

Question VI: Did you find any evidence for HPV by using the electron microscope?

Response: On my 25 cases, there were no case which observed the viral particles by the transmission electron microscope. Therefore, I think that the electron microscope is not effective for the diagneosis of HPV.

Qusetion VII: What are objectives of the surgical treatment?

Response: Complete removal of the tumor is a purpose of the surgical treatment. Incomplete removal of the tumor is the most important factor in this recurrence. If so, more extensive surgical procudures might be expected to be encouraged to decrease the recurrence rate. Although, selection of the surgical procedure depends on the extent of the lesion and the surgeon's preference, the lateral rhinotomy with enbloc ethmoidectomy and medial maxillectomy is the first treatment modality at most institutes. When a diagnosis of carcinoma is established, of course, a more extnesive surgical procedure with or without radiation treatment, should be selected.

Question VIII: How about conservative Surgery?

Response: Preservation of the normal anatomy is very important. Lateral rhinotomy and medial maxillectomy are not appropriate. Its too much. The PV is in the normal mucosa. Iatrogenic spread is possible. Cutting the virus out is not a curative measure. Some inverted papillomas may regress.

Question IX: Radiation therapy?

Response: The PV is a DNA virus. Radiation therapy is a cofactor of multistaged carcinogenesis. I am not in favor of radiation therapy.

Question X : What is the proper lenth of follow-up?

Response: Incidence of recurrence will vary depending on the length and thoroughness of the follow-up investigation. A longterm follow-up is an essential point of the study of papillomas. Most of the recurrences were seen within 3 years after surgery but some have found recurrence 17 years later. Therefore, the length of follow-up investigation should be more than 3 years.

Conclusion : I would like to conclude this conference by mentioning that we have raised the most important questions and comments regarding nasal papilloms, but I believe that other questions and comments still remain that we should work on.

Thank you.

Professor David W. Kennedy M.D., (Chairman), Department of Otorhinolaryngology: Head and Neck Surgery, University of Pennsylvania Medical Center, Philadelphia, P.A., U.S.A.

Professor Heinz Stammberger, University HNO Clinic, Graz, Austria.

Toshio Ohnishi, M.D., Department of Otolaryngology, St. Luke's International Hospital, Tokyo, Japan.

THE ROLE AND TECHNIQUES OF NASAL ENDOSCOPY

David W. Kennedy, M.D.

Endoscopy gives us the potential to bring rhinology into line with the majority of other areas of medicine where treatment is not based primarily or exclusively on patient symptomatology, but rather on careful evaluation of objective findings. The most important role of nasal endoscopy is not the identification of patients for surgical intervention, but rather in the medical management of patients, in the early identification of disease and in the objective evaluation of the response of disease to therapy. Endoscopy is significantly more precise than computed tomography (CT) for the identification of accessible disease, enables accurate cultures to be obtained and the response of the disease to therapy to be assessed. Additionally, since nasal congestion or nasal obstruction in one of the most common symptoms of chronic sinus disease, failure to perform nasal endoscopy may result in unwarranted attention being paid to septal deformities as a cause of this complaint.

The second most important role for nasal endoscopy is in postoperative care. Endoscopic postoperative examination demonstrates the importance of careful local therapy following surgical therapy. It is now clear that most disease which recurs following surgical intervention is not truly recurrent, but rather represents persistent disease which is identifiable endoscopically in the early postoperative period. Indeed, if surgery and careful postoperative care once result in an endoscopically normal cavity, the chances for late recurrence of disease are dramatically reduced. We must therefore work very hard during the postoperative period, both with medical therapy and local cavity care, to maximize surgical results. Areas of persistent localized disease following surgery should alert the surgeon to the possibility of underlying persistent bony osteitis. Additionally, since symptoms can result from single persistently infected ethmoid cells, the surgeon must be particularly observant and meticulous with his postoperative care. The day has gone when a surgeon can look into the nose with anterior rhinoscopy and assume that he has done a good job if the patient is asymptomatic in the early postoperative period and there are no visible polyps present. Endoscopic examination is also essential to the accurate reporting of postoperative results.

The third area in which the endoscopes are helpful is in the selection of patients for surgical intervention. Here the use of endoscopes enables the recognition of persistent disease which does not respond to medical therapy and the

identification of anatomic problems which may predispose to sinus disease. Even with endoscopy however, the CT scan is still required prior to surgical intervention.

The most useful endoscope for diagnostic evaluation is the 30 degree 4 mm. telescope. However, a smaller 2.7 mm. telescope is also required for tight situations. The choice of angle for the smaller telescope is best determined by examiner experience. Whereas the 70 degree telescope provides the best visualization into recesses because of its greater angle of deflection, it is significantly more difficult to pass than a 30 degree 2.7 mm. scope.

In order to make nasal endoscopy time efficient, the head and neck examination should begin with anterior rhinoscopy and the nasal mucosa is then immediately sprayed with a local anesthetic and decongestant. The head and neck examination is completed while the anesthesia is taking effect. After initial anesthesia and decongestion have been obtained, additional anesthesia is obtained by applying further topical on nasal applicators to areas upon which the endoscope may impinge, especially the inferior aspect of the middle turbinate.

An initial pass is made along the floor of the nose to examine the overall nasal anatomy, the area of the inferior meatus and the nasopharynx. Recognition of the nasolacrimal duct is enhanced by gentle pressure on the lacrimal sac. Where an inferior meatal window is present, the maxillary sinus itself may be examined with a flexible endoscope or a 70 rigid instrument. In the nasopharynx, the dynamic action of swallowing on the eustachian tube may be visualized. However, since all the endoscopes have wide angle lenses, there is inherently some degree of "fish eye" effect. This means that extramucosal swellings perpendicular to the telescope appear flattened and extramucosal lesions within the nasopharynx are therefore often better recognized by mirror examination or CT.

A second pass of the endoscope is made between the middle and the inferior turbinate and then medial to the middle turbinate and into the area of the sphenoethmoidal recess. This pass enables visualization of the anterior middle meatus, uncinate process, fontanels and inferior middle meatus. After passing medial to the middle turbinate, the superior meatus and, when possible, the sphenoid sinus ostium were examined. Inflammation, drainage, the presence of mucosal hypertrophy or polyps, anatomic variations and the presence of accessory ostia are all noted. It is my impression that accessory ostia are somewhat akin to tympanic membrane perforations in that they appear to be acquired deformities which occur as a result of a prior infection and ostiomeatal obstruction. These areas of breakdown occur most frequently in the posterior fontanelle and are frequently mistaken for the natural ostium of the maxillary sinus by the inexperienced observer.

A third pass is performed by passing the telescope into the middle meatus. This is typically achieved by rolling the telescope in from below, however, occasionally the middle meatus can be entered from anteriorly. In some instances, entry into the middle meatus is facilitated by gently displacing the middle turbinate medially with a nasal applicator moistened with local anesthetic; a technique which is particularly valuable when the middle turbinate is floppy. When the patient's anatomy precludes the use of a 4 mms telescope, a 2.7 mms scope may be substituted.

In summary, the greatest use of nasal endoscopy is for the objective evaluation of patients undergoing medical therapy. The second most important area for endoscopy in the nose is in postoperative therapy and the third most important area is in the identification of problems requiring surgical intervention. The use of endoscopes during surgical intervention is probable the least important role for these instruments. For, whereas surgery can be performed with other approaches, endoscopic diagnosis is essential for the proper identification of disease. Nasal endoscopy will become the standard of care for the diagnosis of nasal and sinus complaints.

THE ROLE OF NASAL ENDOSCOPY

Heinz Stammberger, M.D.

Rather than talking about new instruments for nasal endoscopy, I would like to further discuss nasal endoscopy itself and its role in current therapy. It is important to stress that endoscopic surgery grew out of the understanding achieved by careful endoscopic observation and diagnosis, and the surgery is essentially a by-product of these observations. Diagnostic nasal endoscopy is therefore a pre-requisite to any surgical intervention. We have been performing diagnostic nasal endoscopy for nearly 40 years and it enabled Messerklinger to study the normal secretion routes and the pathophysiology. As a result of his studies we have come to believe that the mucociliary transport routes are genetically determined and these cannot be changed. Similar predetermined patterns for mucociliary clearance are present in the nose as well as in the sinuses. The use of endoscopes can also enable us to see the interrelationship between sinus and middle ear disease and the effect of sinusitis on eustachian tube function.

Perhaps the most important gain from the use of endoscopes has been further recognition of the importance of the narrow ostiomeatal passages and the importance of these areas to the health of the secondary sinuses. Although this was realized by the early otolaryngologists, the importance had become forgotten until endoscopes again came into use. Subsequently, what we were seeing on endoscopy was confirmed, first by the introduction of polytomography of the sinuses and more recently by the use of CT. Now with these modalities, we have all recognize that it not often necessary to direct our attention to the major sinuses, but rather to direct it to the clefts of the ostiomeatal complex where we so often see the underlying cause of disease. The secondary mucosal changes then usually resolve. To remove only the polypoid disease which presents in the nose is inadequate therapy, somewhat like mowing the lawn. Although the patients symptoms may improve, the polyps will recur unless the deeper areas from which they arise and are also cleared.

The majority of cases with sinus disease can be treated with medical therapy. It is when our endoscopic examination demonstrates that disease persists that we intervene surgically. When we do intervene our primary aim is to only resect the causal area and to perform limited surgery. This is the true advantage of using the endoscopes surgically, they allow us to perform a precise and limited procedure, although we can of course also perform a total sphenoethmoidectomy when this is necessary.

As David said, the endoscopes are crucial for diagnosis. He pointed out how on

anterior rhinoscopy, a septal deformity may appear the be the initial cause of a complaint of nasal congestion when the true cause may be in the ostiomeatal complex. A problem which we see more often is the case where initial examination by anterior rhinoscopy suggests that the problem is caused by large inferior turbinates. Indeed resection of the turbinates may already be under consideration. Closer examination however usually demonstrates another underlying cause for the symptoms and for the turbinate hypertrophy. In some cases the obstruction can be caused by a huge concha bullosa. Following correction of these underlying causes, the inferior turbinate hypertrophy will then often resolve.
In many cases the endoscopes enable us to avoid surgery, to resolve sinusitis by the accurate placement of decongestants to inflamed areas which are resulting in obstruction. We sometimes may do this several times a day, and if endoscopic re-examination demonstrates that drainage is re-established, surgery can be avoided.

Endoscopes also help in our understanding of polypoid sinus disease. Based upon endoscopic examination, I think that we can say that all polyps are not the same and that surgical and medical therapeutic results are dependent on the type of polyp that we are discussing. The more benign types of polyps have localized origin, often from contact areas, such as between the bulla and the sinus of the turbinate. Why these polyps occur in this area, we do not know. It is possible that it is because of poor mucociliary clearance in these areas, it may be because irritative substances collect in these tight areas, or it may be because of the liberation of vasoactive substances from these areas of tight contact. Hopefully, with further research, we sill begin to understand these areas better. Certainly, in many of these cases, removal of the contact areas is curative.

A much more difficult disease to cure are those which originate diffusely, from all areas of the nasal cavity. They usually have a dense, granuloma like, infiltration with eosinophils. The eosinophils are usually degranulated and IGE mediated allergy is typically absent. Whether all of this type of polyps are related arachidonic acid metabolism problems is unclear, but whatever the cause, they are a considerable problem for us and for any type of surgical therapy. They clearly also require medical therapy for control, and I expect that any cure in the future will come from pharmaceutical advances and not from surgery.

A third type of polyp which I might also just mention is the antral choanal polyp. This appears to have a completely different cause and presentation and represents another variant of polypoid disease.

In summary then I would like to re-stress what David has said that the primary role of the endoscopes is for diagnosis. Not Just for inflammatory sinus disease, but also for malignant disease, CSF rhinorrhea. Surgery is purely secondary to these diagnosis possibilities.

ANTERIOR AND POSTERIOR ENDOSCOPIC RHINOSCOPY

Toshio Ohnishi, M.D.

Nasal endoscopy is best divided into anterior and posterior rhinoscopic approaches. The two approaches are complementary.

For anterior nasal endoscopy I prefer a 4 mm. telescope. However with this instrument I frequently have problems visualizing the structures posteriorly. With the anterior nasal examination I can see the anterior nasal septum, anterior middle turbinate, bulla ethmoidale, and middle meatus. Occasionally, it is also possible to see the superior turbinate and the opening to the sphenoid sinus. Inferiorly, nasal endoscopy allows identification of the inferior meatus, and in some cases the nasolacrimal duct.

For posterior rhinoscopy, the 110 degree telescope is chosen and is inserted per-orally to allow examination of the nasopharynx and of the posterior choanae. The eustachian tubes are nicely visualized with this approach. The posterior ends of the inferior, middle and occasionally superior turbinates can easily be seen using posterior rhinoscopy. Additionally, the middle meatus is better seen than from anteriorly. When present, the posterior extent of polypoid disease, drainage from the nose and other pathology in the posterior aspects of the nasal cavity can easily be seen.

Combined rhinoscopy, using both anterior and posterior examination, enables a more complete examination than is possible with either technique alone. In addition to the 110 degree telescope for posterior rhinoscopy, I use a soft palate retractor and a video camera. The type of soft palate retractor which I use is light metal device which rests against the cheek. However, catheters passed through the nose and mouth can also be used. Good topical anesthesia can be achieved with a few sprays of 4% xylocaine. Minimal retraction is used for normal examination, but slightly greater retraction is required when photography is required. However most patients and even older children tolerate this procedure well. In some sensitive patients posterior endoscopic examination may be impossible.

In conclusion combined nasal endoscopy allows a more complete picture of the whole lesion and the entire area of the nose than is possible with anterior examination alone.

DISCUSSION

QUESTION: Do you normally perform the endoscopic examination with the patient sitting or reclining?

DRS OHNISHI AND KENNEDY: We would normally perform diagnostic nasal endoscopy with the patient sitting.
DR. STAMMBERGER: I prefer to perform the examination with the patient lying down. The patient is less likely to move in this position.

QUESTION: What are your indications for performing CT evaluation?
DR. STAMMBERGER: I would perform a coronal CT on all patients going for surgery. This is essential prior to surgery. I would also perform a CT on any patients with a suspected complication, if I see an endoscopic abnormality possibly requiring surgery or if a patient has a strong symptom history suggestive of sinus disease even if the endoscopic examination is normal.
DR. OHNISHI: Any patients going for surgery should have a coronal CT. Since we usually have a delay for CT I would otherwise normally use endoscopy for diagnosis.

QUESTION: Do the panel routinely perform axial CT evaluation?
PANEL: Although the panel do not routinely perform axial CT evaluation, several members of the audience felt that they were helpful in evaluating the anatomy, particularly with regard to the sphenoid sinus.

QUESTION: What is the role of MRI in sinusitis?
PANEL: It is helpful in the differentiation of some soft tissue disease. For instance it helps in the diagnosis of mucoceles and in differentiating tumors from mucus retention. It also helps in fungal sinusitis and in early intracranial disease. The disadvantages of MR are that it does not bone well.
DR. KENNEDY: An additional disadvantage is that the MR is influenced by the nasal cycle. The congested side demonstrates not only mucosal swelling, but also increased T2 resonance which can be mistaken for sinusitis. We performed a study on normal volunteers which demonstrated that these changes also can occur to some extent within the ethmoid sinuses.

QUESTION: There often appears to be some confusion between the symptoms "congestion" and "blockage". The terms often appear to be used synonymously, but this is not really correct. The symptom blockage should refer to poor nasal airflow and congestion to something higher up. Do the panel really differentiate the two symptoms? It appears that this is an area where we should be more precise.
PANEL: It is true that it would be nice to differentiate the two more precisely, but the patient often uses the two terms synonymously and this can be difficult.

QUESTION: When a patient presents with a complaint of headache, how do you differentiate whether this is arising from a nasal source such as a concha bullosa?
DR. OHNISHI: This is a very difficult question for me because in Japan we very rarely see concha bullosa.
DR. KENNEDY: That is very interesting because as some of the audience are undoubtably aware, there are other significant racial differences in sinus disease. Whereas in caucasians, frontal sinus mucoceles are the most common, in Japan it appears that maxillary sinus mucoceles are the most frequently encountered.
DR. STAMMBERGER: I think it is usually possible to differentiate between headache of sinus origin and that from another cause. In the former there is usually a definite intranasal finding and in this case we would correct it. The patient who comes in with pain and pressure between the eyes typically has a problem within the anterior ethmoid area and we would look there particularly carefully.
DR. KENNEDY: I think the diagnosis can be very difficult. It appears that there is probably a spectrum of disease with pure sinus headaches at one end and classical migraine headaches at the other. In between are patients who have some degree of vascular instability, but who may present with predominantly sinus symptoms because, as a result of anatomic or physiological narrowing, they develop sinus obstruction when they get vasodilatation. In this situation a trial of calcium blockers or of beta blockers can sometimes be helpful. Patients with migraine variant headaches will improve, where as those predominantly due to sinus problems will remain the same or get worse.

QUESTION: Is there any place for a screening or limited CT scan?
DR. OHNISHI: This is not something that we do, but it might be worthwhile in terms of saving the patient radiation and expense.
DR. STAMMBERGER: I would disagree. The radiation dose is not high with a CT, and the patient would need a second scan if any abnormality is found.
DR. KENNEDY: I would agree with Dr. Stammberger. The only potential role is in patient follow-up.

QUESTION: Dr. Kennedy, in your presentation you did not stress the third ground lamella. I believe that this is a good landmark, and that limited ethmoidectomy anterior to this is significantly safer for inexperienced surgeons. Would you like to comment on this?
DR. KENNEDY: It is a good landmark. Diagnostically it forms the posterior limit of the middle meatus. However, surgically it can be difficult to identify in some cases. It can be destroyed by moderately severe disease and it can be severely distorted by an extensive sinus lateralis. Occasionally, it can even be displaced all the way back to the anterior wall of the sphenoid sinus.
DR. OHNISHI: I would agree, it is a good landmark, but has many variations and is not always there, so it cannot be relied upon in all cases.

QUESTION: If, during endoscopic sinus surgery, you find polyps in the maxillary sinus, do you do anything about them, such as removing them through the natural ostium of the sinus?
DR. OHNISHI: I typically do a more radical ethmoidectomy, a complete ethmoidectomy and not functional endoscopic surgery. I would try to remove what polyps I can through the widened ostium of the maxillary sinus.
DR. STAMMBERGER: If there were major polyps or cysts present, I would try to grasp any accessible polyps through the ostium, but I would not consider it important to remove every polyp and would not attempt to strip thickened mucosa.
DR. KENNEDY: I vary the size of my antrostomy depending on the extent of the disease. In very severe recurrent of fungal sinusitis I may remove much of the medial wall of the sinus. Primarily, I do this to ensure good mucociliary drainage and ventilation. It also makes the more maxillary sinus disease accessible for removal. However, I do not think it is important to remove all the polypoid disease, just the disease in the area of the ostium.

QUESTION: How many episodes of recurrent sinusitis should a patient have before you think of operating?
DR. OHNISHI: It would depend on the severity of the recurrences rather than the number of recurrences. I also don't think you can rely primarily on the symptoms of the patient.
DR. STAMMBERGER: I would agree that you can't rely primarily on the history of recurrent disease from the patient. I would try to find out why the patient is having recurrences. Is there concha bullosa or some other anatomic abnormality present? Is there allergy requiring treatment or a septal deformity or an immunologic abnormality. If I found something requiring correction, I would correct it when the acute episode has been treated.

QUESTION: Do you use any topical medication, antibiotics or antifungal agents, in the middle meatus or in the maxillary sinus at the time of surgery?
DR. STAMMBERGER: No. Not in any case.

DR. KENNEDY: I regret that we are out of time. I would like to thank the panelists very much for their participation and for your excellent presentations. Thank you very much.

Chairman: ZVONIMIR KRAJINA (Yugoslavia)

Nasal turbinates give a special form to the nasal fossae which is most important in the function - the resistance to the inspiratory and expiratory stream. Besides this, the elements of the tissue, the specific epithelium, the vascular tissue, the mucous glands and nervous structures fulfill the other respiratory and olfactory functions. There are two structures in the turbinates - the bony and the mucosal ones. The bony part gives the shape to the turbinate and mucosa participates mostly in the respiratory and olfactory functions. Asimetry sometimes exists in the turbinates of the left and right side which can be demonstrated by X-ray pictures, tomography or by CT scan. Histological findings show the difference between the inferior and middle turbinate: Vascular elements predominate in the inferior turbinate and mucous glands in the middle one. This can be best demonstrated by PAS method. The mesenchymal elements appear in both turbinates with a prevalence in the middle one which can be of importance in the reactions of the inflammatory changes, especially in the meato-sinus complex. It was demonstrated by Mallory method staining.
Regulatory mechanisms in the respiratory mucosa are mediated by the neural system. Besides the sympathetic and parasympathetic system there exist the neuropeptides (substance P, VIP, neurokinin A, CGRP). Neuropeptides have been discovered and discussed in the last ten years. It is possible that neuropeptides in cooperation with the other two neural components are responsible for the difference between allergic and nonallergic vasomotor shinitis. In the near future the research work should be concentrated in this area.

1. Nils Gunnwar Toremalm (Sweden): Histophathology of the turbinates.
In this short introduction is it not possible to describe in detail the normal and pathological histology of the turbinate bone structures and the different soft tissue layers: the mucosa, submucosa and periostal layers. However, histopathological examinations are of great clinical value and have also been the object of numerous experimental investigations on animals and human beings. What can histopathological studies of the turbinates be useful for clinically and experimentally?
Clinical histopathology: 1. Biopsy examination in combination with functional studies of the mucociliary activity are valuable in cases of chronic rhinitis and suspected Kartagener's triad or cystic fibrosis.
2. Chronic infections due to viral toxins and proteolytic enzymes released from leucocytes.
3. Effects of air pollutants and chemical substances including pharmacs for local application. 4. The differential diagnose between allergic and non-allergic vasomotor shinitis is sometimes difficult. The presence and distribution pattern of neuropeptides and neural receptors may perhaps solve this problem in the future with the use of histological methods.
5. Degenerative and malignant processes cannot be diagnosed without histology.
Experimental histopathology: 1. Normal versus abnormal distribution of different cell types of the mucosa are not easy to evaluate due to the fact that everyone is more or less exposed to recurrent viral infections, air pollutants etc. Furthermore, most of the air flow passes over a relatively small percentage of the surface which may have influence on the results.
2. Experimental exposures to different air pollutants, viral and bacterial toxins, as well as tobacco-smoke, have been carried out in many laboratories with sometimes inconsistent results. The imbalance between the common enzymes (elastase and collagenase) and their specific inhibitors are of great interest.
3. Industrial exposure e.g. for nickel and wood dust has been closely examined. 4. Studies of the allergic mechanisms, for example the distribution and degree of degranulation of mast cells in the nasal mucosa have been the aim of many recent studies. 5. The biologic background and development of nasal polyps is still a matter of dispute and further experimental studies are needed regarding genetic, environmental, hormonal and other factors. 6. The presence and interrelationship between adrenergic, muscarinic and other neural receptors is a field where we only have seen "the top of the iceberg." 7. Therapeutic effects of new pharmaca for nasal application are naturally thoroughly investigated before introduction but more has to be done regarding suggested late side effects on the nasal defence mechanisms. 8. The art and degree of histopathological changes following different techiques for turbinate surgery are of interest. The list of experimental histopathology could be made even longer but I have stop here.

Summary:
In dealing with histopathology of the turbinates I find it necessary to point out that clinical rhinologist must be acquainted with modern histological techniques regarding fixation, staining, immuno- and radio-assays. It is also necessary to point out that

histopathological examinations must be supplied by other morphologic and functional investigations such as X-ray, sonology, allergy, screwing and provocations, mucociliary transport, rhinomanometry etc. Obviously there is still a great need for further innovative investigations within this deeply interesting of field Rhinology.

2. Ranko Risavi (Yugoslavia): CO2 laser turbinatomy in the treatment of vasomotor rhinopatia

We based our study on a group of 115 patients (67 females and 48 males) aged 16 to 52, suffering from non-allergic or allergic vasomotor rhinitis. Prior to the intervention, all the examinees had difficulty with nasal breathing and had been treated with drugs.
Each patient's anamnestic data was taken with a special reference to nasal breathing difficulties, secretion, the frequency of symptoms and duration of illness.
Apart from the standard ENT examination, an endoscopic nasal inspection was performed. In order to establish the acquired sensitivity to inhalative allergens.
Prick and RIST tests were done, prior to the operation.
During the first examination as well as 3 and 12 months after the operation, Rhinomanometry was performed with the use of a Mercury RN6 Rhinomanometer at the fixed oressyre if 150 Pa.
A cytological smear of the nasal mucus was taken from the front pole of the inferior nasal turbinate. The smear was considered positive of there was the presence of goblet cells in the optic field with large quantity of esinophilia, few mastocytes, some neutroohils, a small number of cylindrical cells, a naked nucleus and considerable amount of clear mucous. During the saccharine test performed by applying a saccharine granule weighting 3-5 mg to approximately 1.5 cm of the front pole of the inferior nasal turbinate, the patient remains seated and is not forced to swallow. The sweet taste in the pharynx appeared 8-12 minutes after placing the granule in the nose was considered a normal result for the maco-ciliary transport. The CO2 laser turbinotomy was applied using the Sharplan 1020 with power setting of 12 W and a power density of 200/W/cm2 combined with a surgical microscope. Punctiform incisions were made on the front pole of the inferior nasal turbinate and at the free edge of the hypertrophic mucous membrane of the middle and partial back part of the nasal turbinate as posteriorly as possible.
In the statistical analysis the Wilcoxon's sign test was used to test the difference in individual resistance (Rn) and total nasal resistance (TRn) during inspiration and expiration. Friedman's analysis test for non parametric specimens was used in order to test the differences of the same parameters 3 and 12 months later.
The results of Prick testing to establish the acquired sensitivity to inhalative allergens in 90 patients and the result of RIST testing in 84 were negative. The normal cytological level of the nasal mucus was found in 62 examinees, and the result of the saccharine test showed normal values in 77 patients.
The improvement in nasal breathing by anamnestic data 3 and 12 months after the operation are shown on table 1.
The rhinoscopic and endoscopic examination showed the normal appearance of mucus and reduced secretion in 91 (79.1%) 12 months after the operation. Normal cytological levels were found in 99 (86.1%), and the results of saccharine testing were within the normal boundaries in 104 (90.4%) of cases. Rhinomanometric testing done before turbinoctomy showed increases value of Rn and TRn during ins. et exp. with all the patients. The testing of difference of separate parameters Rni, Rne, TRni and TRne during the observation period of 12 months after operation showed a significant reduction in Rni and Rne values for both left and right nose (tables 2, 3). The submucosal septoplasty together with the laser turbinotomy was performed on 31 patients.
During CO2 laser incisions release the extracellular fluid from the freed space in the submucosis, causing the evaporation of tissue and thus, reducing the edema. The carbonisation of the tissue appears on the edges of the sensitive surface, reducing the possibility of secondary infections. The coagulation caused by the application of defocused beam in blood vessels of 0.5 mm causes hemostasis. The listed procedures lessen the pain, quicken the healing process and make the postoperative tamponada practically unnecessary. The reparation of the ciliary epithel appears, the blood vessel lumina are normalised and their number reduced. As a result, a fibrosis in the submucus appears primarily around the nasal glands and small blood vessels. These changes are probably caused by the heat involves in CO2 laser therapy.
It is very useful, with submucosal septoplasty, to apply the laser turinoctomy in cases involving vasomotoric change sin the nasal mucosa. Breathing is significantly improved with the removal of the mechanical obstructions caused by a deviation or fracture of the nasal septum.

3. C. F. Lin (Taiwan): Submucosal diathermy and defocused CO2 laser surgery

Traditionally, medical treatment, such as drug therapy and immunotherapy, has always been the primary treatment for allergic rhinitis. However, for some

more severe cases, surgical treatment is another good choice. Clinical articles have suggested that both submucosal diathermy and defocused CO2 laser surgery are effective in treating allergic rhinitis.
72 patients in total were proven to be rhinitis allergic by either nasal eosinophilia or positive skin test. 42 of them were treated with submucosal diathermy, whereas 31 with defocused CO2 laser surgery. Electro-surgical unit and bipolar submucosal turbinate probe were used in submucosal diathermy with a current intensity of 4-5 watts and exposure time of 5-10 seconds. On the other hand, Sharplan laser connecting to a special-designed handpiece with a reflected type nasal pipe, releasing laser beam at a pulse mode of 15 watts intensity and 0.1 second exposure time over the entire surface of each inferior turbinate.

Results are:

1. 47% of patients were found improved by submucosal diathermy; individual symptom concerned, 88% claimed improvement in nasal blockage.
2. 84% of patients were found improved after defocused CO2 laser surgery; individual symptom concerned, over 80% of patients improved in nasal blockage.

Both submucosal diathermy and defocused CO2 laser surgery formed fibrosis, but the real mechanism of why laser surgery is more effective in treating allergic rhinitis than submucosal diathermy is still left open for us to explore.

Discussion

Questions:

1. Z. Krajina (Yugoslavia)
   1. From the ethycal point of view are the frequent biopsies of the nasal mucosa faithful?
   2. Using the laser in the treatment of allergic rhinitis, the question is in which forms of new allergic or how allergic rhinitis this kind of treatment is indicated?
   3. About nasal eosinophilia the question is what differences exist between allergic and non allergic cases?

2. T. Sekitani (Japan)
   1. How the incidency of rhinitis medicamentose rises in Sweden due to the use of nose drops?
   2. Is there a specific chemical compounds of the nose drops content?
   3. In relating to hypertrophied rhinitis or "stuffy nose" in the aged group, we should like to care some prescription of dome drug for hypertension. What do you think or what is your experience?

To dr. Lin (Taiwan) 4. Do you have another special type of the laser probe than that which you showed in the slide. If you used that type of the probe, you and we cannot vaporize or cauterize deep into turbinate? Most important point is the posterior portion of inferior turbinate.

3. N. G. Toremalm (Sweden)
   For how long were these patients medically treated before laser?

4. V. I. Marokhoev (USSR)
   What is your opinion about implantation autologous cartilage into inferior turbinate in the atrophic rhinitis?

Answers: were given by Krajina, Toremalm, Lim and Rivsavi:

1. Ethics: There are no problems in daily clinical work but naturally they may arise when we make experimental investigations.

2. Submucosal diathermy is indicated in vasomotor rhinitis and CO2 laser surgery for allergic rhinitis. The fibrosis in the superficial layer is evident in 1 month after CO" laser.

3. Eosinophilia is very abundant in allergic rhinitis not only locally in the nasal mucosa and very often combined with blood eosinophilia. In vasomotor rhinitis eosophilia can be present but not so pronounced.

4. The number of patients with nasal problem is increasing in some parts of the world. Many people are especially suffering from blocked noses with little permanent relieve even after extended use of locally administered pharmaca and therefore new approaches for a more radical treatment has become a unique challenge to modern rhinologists.

5. The diagnose "Rhinitis medicamentoda" has again been a reality. The consumption of decongestive nose drops in Sweden has increased more than 100% between 1988 and 1990 and our colleagues are becoming more and more aware of this problem.

6. Relating to stuffy nose in hypertensive patients the doses for hypertensia should be reduced or combined with local treatment with steroid drops.

7. We used only this type of the probe for submucosal diathermy and could reach to posterior part of the lower turbinate. In extreme cases the probe can be applied more posteriorly.

8. The patients were medically treated between 6 months and 1 year before laser application.

9. Autologous cartilage was used into inferior turbinate in the atrophic rhinitis with good results. Sometimes later or this cartilage was reduced but not totally.

FIRESIDE CONFERENCE 6 IMMOTILE CILIA SYNDROME AND SINOBRONCHIAL SYNDROME

1. Introduction (V. Jahnke)

Regarding the terminology, it is pointed out for a common language that the immotile cilia syndrome is synonymous with ciliary dyskinesia and that the immotile cilia syndrome occurs in two forms: a) primary (inherited by an autosomal recessive trait) with or without situs inversus. Kartagener's syndrome is characterized by the triad situs inversus, bronchiectasis and recurrent sinusitis; however, using tannic acid staining, it has been shown that in Kartagener's syndrome the ciliary fine structure may be normal while the ciliary movement is impaired. A rare special entity is the nasal acilia syndrome characterized by complete absence of cilia. b) secondary (acquired) due to chronic infection. The diagnosis of the immotile cilia syndrome is established by transmission electron microscopy, showing characteristic fine structural defects.
The sinubronchial syndrome is defined as a coexisting pathology of chronic sinusitis and chronic nonspecific inflammatory lesions of the lower airway such as chronic bronchitis, bronchiectasis and diffuse peribronchiolitis (the latter being known only in Japanese people). It is estimated that 10% of the patients with chronic sinusitis have the sinubronchial syndrome and 50% of patients with lower respiratory infectious diseases. The question remains whether a causal relationship or common basis exists between bronchial asthma and sinusitis. There is no doubt that physiologic and pathophysiologic relationships exist between upper and lower airways and that neural and humoral events occur. There are also interesting aspects of allergy, hyperreactivity and the problem of endonasal polyps, aspirin intolerance and bronchial asthma.

2. Mechanism of Ciliary Beating (H. Mohri)

The speaker clarified the details and ultrastructure of ciliary activity. The ultrastructure of flagellae and cilia is nearly identical. Two central single microtubules are surrounded by nine outer doublet microtubules, well known as 9 plus 2. Each of the outer doublets consists of a complete A-tubule and a C-shaped B-tubule. The outer and inner arms are projecting from the A-tubules to the B-tubules. The radial spokes are the structures attaching the outer to the central doublets, the connection between the outer tubules are formed by nexin or interdoublet links. A ciliary membrane surrounds this structure called axoneme.
Characteristic for the ciliary and flagellar movement is the sliding with the aid of arms between the adjacent doublet microtubules. These arms consist of axonemal dynein ATP-ase with two or three heads which are connected to the outer doublets. Dynein, with the molecular weight of 1200 to 2000 KDa contains two or three heavy chains, two or three intermediate chains and several light chains. The inner and the outer dynein arms are different from each other, both are able to support the microtubule sliding. The dynein arm bindings to the B-tubules are ATP-dependant, the bindings to the A-tubules are ATP-independant. The conformation of the dynein molecule is changing during ATP hydrolysis in the state of dynein-ADP-Pi. This change seems to be responsible for the conversion of released chemical

energy into the mechnical energy of the microtubule sliding. The conversion of the microtubules during ciliar or flagellar movement has not yet been sufficiently described. It could be assumed that several other structures than dynein participate in this process of bending. The central doublets rotate when they are freed from the axoneme. A special species of dynein in the axoneme seems to obtain the rotation of microtubules.
One of the causes of the ICS is the inherent lack of dynein arms. Chemical removal of dynein arms as an experiment induces reduction of beat frequency and the speed of microtubule sliding, immotile cilia or flagellae are the result. It is stressed that other structural defects of the axoneme are also able to cause the ICS.

In the discussion, the speaker pointed out 1. he did not study mammalian cilia or flagellae; 2. outer and inner arms consist of two different molecule species, both of them have the ability for a sliding mechanism; inner arms are more complex, and after removal of outer arms the sliding mechanism is still possible; 3. if the ultrastructure is normal, but the motility abnormal, one can speculate that this is due to a metabolic cause, particularly at the root.

3.Immotile Cilia Syndrome (M.Kawakami)

The immotile cilia syndrome (ICS) is defined as an inherited disorder, characterized by inappopriate motility of cilia in airways and other organs, and in sperm tails. Studies of ICS -specimen of the respiratory epithelium show different findings in detail.Totally immotile cilia, inappropriate beats, low beating frequency or asynchrony are observed. This reduced function causes the well known clinical symptoms. For establishment of the diagnosis ICS ultrastructural examinations of the epithelium and the cilia are necessary. Cilia in the ICS often have defects of the outer or inner or of all dynein arms. Other characteristic findings are short outer dynein arms, missing radial spokes and microtubular abnormalities in number or arrangement. A reduced mucociliary transport is not only due to structural abnormalities, but the bronchial and nasal mucus is also an important factor. For the better understanding of the ICS the bronchial mucus must be investigated; the different parameters included spinnability, yield value, viscoelasticity , adhesiveness, concentrations of albumin, fucose, sialic acid, IgA, IgG and phospholipid composition. In comparison to patients with chronic respiratory disease without ICS identical results were found. The sputum placed on the frog palate showed a normal transport. It was concluded that the sputum does not seem to play an important role in the mucociliary transport impairment in the ICS.
In the discussion it was pointed out that transmission electron microscopy is essential to diagnose the ICS, though it is not always sufficient; lack of inner arms or both inner and outer arms occurs in more than 90% of ICS and in about 50% of chronic sinusitis; The examination which is time consumming, requires 5-6 areas in the nose, each of them in 10 blocks; in the ICS one has to examine the tracheal and the bronchial mucosa because in the nose metaplasia is common.

4. The Ciliary Beat Frequency and Impaired Mucociliary Function in Chronic Respiratory Diseases (J. Nuutinen)

Impaired mucociliary function is a common finding in patients with chronic respiratory symptoms as in sinusitis, bronchitis or otitis media. The function and structure of the respiratory mucosa in the sinuses, the bronchial system, the nasal cavity and the Eustachian Tube is the same. Diseases in these areas have to be considered as one unit. The reduced effectiveness could be caused by the changes in the ciliary beat frequency, the ciliary structure, the amount, composition and viscolelastic character of the mucus or properties of the interciliary fluid.
Nasal mucociliary function was measured in 150 patients suffering from otitis media, rhinitis, sinusitis and chronic bronchitis and in 26 healthy persons with a radioisotopic method. The used tracer included Tc 99m and was applicated into the nasal vestibule. After measuring the time of transport to the oropharynx the nasociliary transport velocity was calculated. This is a painless method with a minimal radiation dose which messures all ciliary functions such as ciliary beat, mucus and ciliary structure The possibility of measuring bronchial ciliary transport by inhalation of the tracer was mentioned. The ciliary function of the Eustachian Tube could be shown by application of the tracer into the middle ear after tympanotomy. Measurements were only done in the absence of acute infections. The mean nasal mucociliary transport rate was 9.0mm/min in healthy persons, 4.0mm/min in the total patient material and 2.3mm/min in cases of chronic bronchitis A follow up study showed that nasal mucuciliary velocity is well correlated with the mentioned clinical symptoms and suitable for diagnostic studies.
The ciliary beat frequency (CBF) was measured with a photoelectric method in vitro in 150 patients. The most common symptom was chronic or recurrent sinusitis. CBF was examined in the normal of the maxillaris sinus, sphenoidal sinus and mastoid antrum. A significant correlation was shown between clinical findings and the CBF which was reduced concerning the patients with chronic bronchitis.The ultrastructure of the respiratory epithelium was not pathologically changed in all of those cases; this was interpreted as evidence of a multifactorial etiology of sinusitis.
Regarding the relationship between upper and lower airways the speaker pointed out that in chronic pulmonary disease the nasal mucociliary function is lower than in healthy subjects; he also remarked that "the nose is that part of the lung that can be reached with a finger" and that "the lungs are the lowermost paranasal sinuses".
In the discussion the speaker reported some cases which have shown significant differences in the mucociliary transport between the left and the right nasal cavity because the nasal cycle affects the transport. Therefore in his opinion it is necessary to investigate both nasal cavities for the diagnosis of a ICS which is only possible with a Tc 99m technique.

During the general discussion the value of transmission electron microscopy and scanning electron microscopy was compaired: With scanning electron microscopy, large areas can be studied as well as the length of the cilia; in the future this method may be used more frequently for immunological markings. Using transmission electron microscopy, inner dynein arms often are not possible to see so that a combination with functional tests is recommended; the difference between primary and secondary ICS can be made by cell-culture.

FIRESIDE CONFERENCE 7 IMMUNOTHERAPY FOR ALLERGIC RHINITIS

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The immunotherapy fireside conference began with three introductory lectures, which were then followed by a general discussion.

Dr. Naclerio discussed studies with a seasonal allergen, ragweed. He began by reviewing a clinical trial performed by Philip Norman in the late 60s. The study illustrated the increase in nasal symptoms induced by natural exposure to ragweed pollen. It also showed how ragweed immunotherapy significantly blunted this symptomatic response. Instead of presenting additional studies supporting the efficacy of immunotherapy, he focused his discussion on the effect of aqueous ragweed immunotherapy on the inflammatory response to nasal challenge with antigen.

The nasal response to antigen stimulation of a ragweed-allergic subject begins with an early reaction occurring within minutes and is then followed hours later by an inflammatory late phase reaction. The early reaction occurs universally and is dominated by mast cell degranulation. The late reaction is more variable. Four aspects of the late response were discussed: cellular infiltration, priming, late phase reactions and hyperresponsiveness to irritants.

All studies employed a standard approach to treatment. The subjects began receiving injections with a low dose of extract which was slowly increased to a maintenance dose over a three-month period. This approach caused some local and some systemic reactions, but over 95% of the subjects were able to reach the maintenance dose.

Immunotherapy favorably shifted the dose response curve between ragweed pollen exposure and the immediate symptomatic response and mediator release. The effect of immunotherapy on cellular infiltration was demonstrated both following nasal challenge and during the season. The percentage of eosinophils before and 24 hours after nasal challenge was compared at different doses of immunotherapy. Subjects receiving no treatment had the greatest increase in eosinophil percentage, while those on treatment had a significantly smaller change. A high maintenance dose, 24 mcg of Amb a I, was more effective than a modest dose, 2 mcg of Amb a I. Similar findings occurred in studies performed during the season, i.e., immunotherapy reduced the percent increase in eosinophils and a higher maintenance dose was more effective. The late and priming reactions, each of which has an incidence of about 50%, were partially blocked by immunotherapy. The reduction in the late and priming reaction always occurred in coordination with a reduction in the antecedent early reaction. Hyperresponsiveness was evaluated by performing nasal challenges with histamine before, during and after the season. The no treatment group showed increased responsiveness to histamine at the peak of the season, but this appeared to be more of a shift in baseline responsiveness than a true hyperreactivity to histamine. Regardless of the interpretation, immunotherapy blocked this reaction.

Accompanying the nasal response, though not correlating with it , were immunologic changes in the serum. The initiation of immunotherapy led to a slight rise in ragweed-specific IgE antibodies and a dramatic increase in the levels of ragweed-specific IgG antibodies. Immunotherapy also prevented the seasonal rise in ragweed-specific IgE. Although the exact mechanism by which immunotherapy achieves its clinical efficacy remains obscure, it has profound effects on the nasal response to natural and induced pollen exposure.

Dr. Otsuka presented his investigations on the mechanisms of immunotherapy. In contrast to the studies with a seasonal allergen, he examined a perennial allergen, crude house dust. He focused on three mechanisms: the number of mast cells in the nasal mucosa and their releasability, the development of IgG_4 blocking antibodies and the sensitivity of the nasal mucous membrane to histamine.

The protocol for the administration of immunotherapy was based on skin test sensitivity but usually began with 0.25 ng. The injections were given twice weekly and increased by 50% until the maintenance dose was reached. After the maintenance dose was reached, in about three months, the injections were spread out to once a week for four weeks, then once every other week for eight weeks, then to once a month.

The subjects showed increases in the serum-specific IgG, but there were no differences between the group of subjects with a good clinical response and those with a poor response. Similar results were found when the IgG_4 subclass was determined. Dr. Otsuka next examined metachromatic cells in the nasal epithelial layer. These cells were increased in subjects with nasal allergy compared to normal subjects. The treated group showed a significant reduction in the number of these cells as well as the histamine content of the epithelium within three months, particularly in those subjects with a good clinical response. The *ex vivo* release of histamine following antigen stimulation from the metachromatic cells showed no significant differences between treated and nontreated subjects. The nasal response to histamine stimulation of the inferior turbinate tended to decrease at 12 months, but no statistically significant changes were observed between groups. Dr. Otsuka speculated that the changes in the number of metachromatic cells is an important mechanism for successful immunotherapy.

Dr. Horack next reviewed our current knowledge about oral hyposensitization. He began by stating that the goal for any type of immunotherapy should be the shortening of the time period in which a patient has serious complaints combined with a reduction of the need for symptomatic pharmacotherapy. Oral hyposensitization has a long history. The first published report was in 1922 by M. D. Touart. Most trials were not controlled, and those that were showed limited efficacy. Some general trends were seen: 1) birch pollen led to greater efficacy than grass pollen; 2) children did better than adults; 3) sublingual treatment appeared superior to drops and 4) effective therapy needed a high total dose. A marked variation in the rate of denaturation of the allergens and the rate of allergen release are two important factors for successful treatment.

Dr. Horack then described his experience comparing conventional immunotherapy, subcutaneous immunotherapy combined with oral desensitization, and placebo. Both active treatments were better than placebo. The possibility of home use is the major argument favoring oral immunotherapy, but its safety remains to be determined. In Dr. Horack's experience, both local and systemic reactions occur. He concluded by emphasizing the need for more information to be obtained from controlled clinical trials before deciding whether oral hyposensitization is a practical option.

A general discussion followed. The first area discussed was additional mechanisms of action. Besides the changes mentioned above, other investigators have shown changes in nasal antibody levels, in cytokine production and T cell subsets following immunotherapy. The rapid reduction in the nasal response to antigen provocation occurs before changes to serum antibody levels, questioning the role of blocking antibodies as the sole mechanism of action. Most likely, many mechanisms contribute to the effectiveness of immunotherapy, but further research is needed in this area.

Most clinicians offer patients immunotherapy if they have failed pharmacotherapy. No one, however, could cite a study supporting the effectiveness of immunotherapy in this situation. Additional indications included the need for large doses of medications, increasing symptomatology over the preceding year, the occurrence of seasonal asthma, and Olympic athletes who cannot compete if they take intranasal steroids. Other considerations included the duration of symptoms throughout the year, the number of antigens to which a person is sensitized, the intensity of antigen exposure, the presence of chronic asthma and the ability to comply with the therapy.

The regimens for treatment tend to show uniformity across the continents. Most begin with a low dose and increase it at weekly intervals until a maintenance dose is obtained, usually in about three months. The maintenance dose should be the highest tolerated dose and is usually given at monthly intervals. The European community avoids aqueous extracts and prefers hydroxide depot injections because of a lower incidence of systemic reactions. In rare instances, a rush regimen can be devised to shorten the time interval from initiation to maintenance therapy. This regimen, however, increases the risk of side effects. Caution was raised about altering the regimen of immunotherapy during the peak of the pollen season. Most deaths from immunotherapy occurred in asthmatics during pollen seasons. The issue of safety, i.e., the deaths reported following treatment, led to the virtual abandonment of immunotherapy in England. When treating a disease of limited morbidity, such as allergic rhinitis, the risks of the treatment should not exceed those of the disease.

While there were minimal data to support the position, a consensus felt that a minimum of three years was necessary at the maintenance dose. In the literature, Dr. Patterson suggests that stopping after five years produced three groups: those subjects who were cured, those who required minimal pharmacotherapy and those who reverted to significant problems. Dr. Otsuka described a questionnaire study that he performed. Patients stopping immunotherapy before two years of treatment fared no better than patients receiving no treatment. Patients receiving treatment for greater than three years did the best regarding the use of medications and emergency visits to the hospital. Dr. Horack also felt that treatment must be continued for at least three years. He bases the decision to stop on whether the patient's condition continues to improve or has stabilized.

Many issues remain. What are the best extracts? Can modifications of antigen preparations increase immunogenicity, while decreasing allergenicity, the cause of side effects? Will we be able to suppress the IgE-specific T cell response, as can be done in mice? Can one develop IgE antibody to bacterial products? Should we treat newborns at high risk of developing allergic disease? Does successful treatment affect the incidence of acute sinusitis or alter the course of chronic sinusitis? How long do you attempt to treat a patient before considering treatment a failure? Can the oral or nasal route of antigen administration be improved to permit the patient to deliver his own therapy? Can we monitor any parameter to predict successful outcomes? These

are only part of the issues that deserve further study. As long as immunotherapy is perceived as the only treatment for allergic disease which can favorably alter its natural history, investigators will continue to study its mechanism of action and its optimal treatment regimen.

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Chairman: B. Drettner, Sweden,
Co-chairman: S. Sakai, Japan
Speakers: D. Howard, UK, L.P. Löbe, Germany, G.A. Sisson, Chicago, USA

INTRODUCTION

Cancer statistics show that in the Scandinavian countries cancer of the nose and paranasal sinuses has decreased considerably during the last decades and more so than for any other kind of cancer. Simultaneously this decrease has tended to occur mainly among highly differentiated squamous cell carcinomas while the incidence of low differentiated carcinomas has remained unchanged. Today cancer in the nose and paransal sinuses is very rare in Scandinavia. However, reports from England and Germany indicate that such a decrease has not yet been seen in these countries. One possible explanation for the decrease in Scandinavia could be a decreasing incidence of chronic sinusitis.

The treatment of cancer of the nose and paranasal sinuses has changed during the last few decades. In Japan chemotherapy is used more than in other parts of the world. Craniofacial surgery is more and more frequently used for some of these cancers.

CASE REPORTS

1. Professor Sakai presented a case report on a 73 -year -old man with a moderately differentiated squamous cell carcinoma in the right maxillary sinus and with a metastasis in the right submandibular region. The tumour was classified as T2N2aM0 by UICC (1987). The patient was given 50 Gy of radiation, an extensive Denker operation and a radical neck dissection were performed. He has been free from tumour for 4 years. There were no great controversies among the panelists as to treatment of this patient. Complete maxillectomy was suggested as an alternative to extensive Denker operation. The majority of the panelists seemed to prefer preoperative radiation.

2. Doctor Sisson presented a case of adenocarcinoma in whom he had performed a craniofacial resection. He also gave a history of this procedure and mentioned that he did his first craniofacial resection as early as in 1963. He also presented another case in whom craniofacial resection for various reasons was refused but the patient lived for 11 years with growing tumour and died from other disease without any operation. Adenocarcinoma seems to constitute about 9%-10% of all malignant tumours in the nose and paranasal sinuses.

Doctor Howard mentioned that about half of all adenocarcinomas have a wood dust exposure and that those who also are smokers have 3-4 times higher incidence. There is still much to do concering preventive efforts in furniture industry in order to reduce the amount of wood dust. A combination of craniofacial surgery and radiotherapy has improved the survival rate.

3. Doctor Howard reported a case of olfactory neuroblastoma with only small symptoms consisting of epistaxis and a unilateral nasal polyp. MR showed an extensive tumour in the nose and paranasal sinuses extending to the cribriform plate. Pathological diagnosis was highly differentiated olfactory neuroblastoma. All the panelists suggested craniofacial surgery and radiotherapy while the attitude to chemotherapy varied, and no one could give any conclusive recommendation. The postoperative photographs showed almost no scar and definitely no deformity of the face in spite of the extensive craniofacial resection. It was also stressed that many of these patients are very young when they get this kind of tumour.

4. Professor Löbe presented a 46-year-old man who had T4 squamous cell carcinoma in the nasal roof area with infiltration of the skin. He was treated with a primary resection and reconstruction, and with postoperative irradiation with 60 Gy. Six months later the carcioma recurred in the nasal roof area with infiltration in both orbits as well as both eyeballs verified by ophthalmological investigation and CT scan. The patient was prepared to sacrifice both his eyeballs in order to survive. The therapy discussion among the panelists ranged between from no kind of treatment to palliative chemotherapy and/or additional radiotherapy. Doctor Löbe had performed an operation where the right eyeball was resected but the left eyeball could be preserved, followed later by reconstructive procedures. The patient has now been free from disease for 5 years. Doctor Howard pointed out that it was probably very rare that surgery was successful in such cases.

Treatment policies

Treatment in Japan (S. Sakai)

Professor Sakai made a retrospective evaluation of 33 years' experience of treatment of maxillary sinus carcinoma (Fig. 1a). The cumulative survival rate for the four periods increased from 20% for the first period to 46% for the latest period (Fig. 1b). The frequency of maxillectomy was reduced from 40% in the first period to 19% in the latest period. The present way of treatment is presented in Fig. 1c.

Fig. 1. Treatment policies, survival rate and present mode of treatment according to Professor S. Sakai.

FIG 1a

SUBJECTS AND TREATMENT POLICY

845 cases of maxillary sinus carcinoma treated 1957 – 1983

282 cases in 1957 – 1966
RT 70Gy/7wk, Maxillectomy

191 cases in 1967 – 1971
RT 70Gy/7wk, 5-FU intraart. Infus.

168 cases in 1972 – 1975
RT 50Gy/5wk, 5-FU intraart. Infus., Curettage or extensive Denker's op.

204 cases in 1976 – 1982
RT 50Gy/5wk, 5-FU inteaart. Infus., Curettage or extensive Denker's op., Cryosurg., Immuno. Therapy

Since 1967, Maxillectomy when it recurs

FIG 1b

CUMULATIVE SURVIVAL RATES BY CHRONOLOGICAL GROUP OF 845 CASES (1957-82) OF MAXILLARY SINUS CARCINOMA

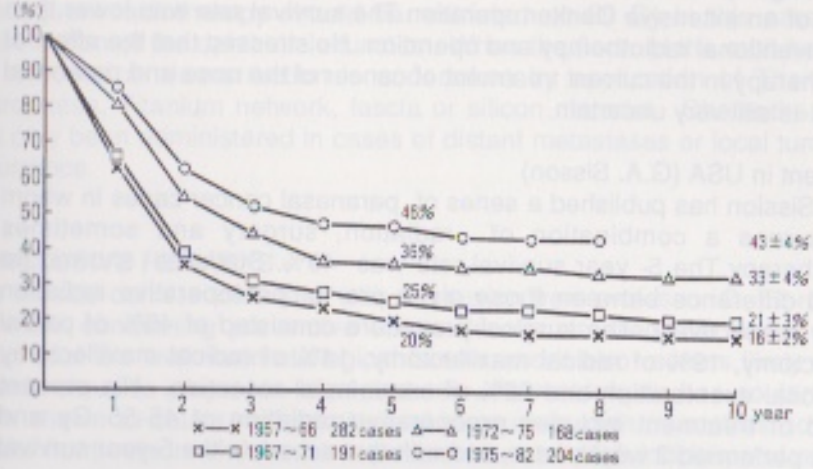

FIG 1c

COMBINED TREATMENT FOR MAXILLARY SINUS CARCINOMA AT PRESENT

1. Radiotherapy with 50Gy/25fr/5wk
2. Continuous intraart. infus. of 5-FU 2,000mg/4wk
3. Antrostomy and cleaning the maxillary sinus
4. Cryosurgery once a week, if possible
5. Extensive Denker's operation 2-3 weeks later
6. Maxillectomy when it recurs, it resists RT, or it extends as T4 but it's still operable

Cerebral bleeding or cerebromalacia was a predominant cause of mortality in the early period and the focus was always on the same side as the maxillary cancer indicating a late radiation effect. Another side effect was visual impairment, not only on the affected side but also on the other side resulting in only 66% of patients having good visual acuity. Both these side effects seem also to be a result of a very high dose of irradiation which now has been reduced. In the discussion professor Sakai was not in favour of a very low dose of irradiation combined with topical treatment with chemotherapy which has been suggested by other Japanese doctors.

Doctor Howard mentioned that in the 1970 when professor Sakai´s results became known in the Western world a series of 60 consecutive patients were operated on in London according to professor Sakai´s method. The only change in treatment was that a total maxillectomy was performed instead of an extensive Denker operation.The survival rate was lower than with conventional radiotherapy and operation. He stressed that the effect of chemotherapy in the current treatment of cancer of the nose and paranasal sinuses is still very uncertain.

Treatment in USA (G.A. Sisson)
Doctor Sission has published a series of paranasal cancer cases in whom therapy was a combination of radiation, surgery and sometimes chemotherapy.The 5- year survival rate was 49%. Statistics showed no survival difference between those given pre- or postoperative radiation therapy respectively. The surgical procedure consisted of 45% of partial maxillectomy, 19% of radical maxillectomy, 14% of radical maxillectomy with orbital exenteration and 22% of craniofacial resection. His present method of treatment includes preoperative radiation of 45-55 Gy and surgery performed 2 weeks later, and with that schedule the 5-year survival rate has now risen to 65%.

Treatment in England (David Howard)
There is usually good agreement concerning treatment of maxillary carcinoma. However, when the tumour extends to the ethmoidal area with invasion of the orbit, including the periostium, the therapeutic modalities are in much more controversy. The classical kind of treatment with lateral rhinotomy or a total maxillectomy with orbital exenteration caused a high incidence of local recurrences, particularly in the anterior fossa floor and especially in adenocarcinomas. Craniofacial resection offers a better way of approaching this area and does not entail disturbing scars, deformities or removal of the orbit or eyeball. Doctor Howard also emphasized the value of MR in order to differentiate between tumour and inflammation and retained secretion.

The survival rate was about 40%, but for olfactory neuroblastoma it was almost 70%. There was no obvious difference in the survival rate related to pre- or postoperative irradiation.

Treatment in Germany (L.P. Löbe)
For squamous cell carcinomas T1 and T2 the therapy starts with operation while for T3 and T4 radiotherapy (60-70 Gy) may be the first step before operation. Very limited T1 tumours of the nose and ethmoid sinus are resected with the endoscopically or microscopically controlled endonasal approach partly by the use of CO_2 Laser. For bigger tumours the incision by Moure or Zange is used. Orbital exenteration was not suggested as a treatment modality in any case of orbital penetration since an attempt is made to preserve the ophthalmic function if possible. The orbital soft tissue is carefully dissected up to the oblique and rectus muscles as extensively as necessary with the help of the operating microscope and intraoperative frozen section examinations. For preservation of the eyeball the subsequent radiotherapy should be restricted to 30 Gy in this area for preservation of the ophthalmic function. When the floor of the orbit has to be removed a reconstruction is undertaken by application of Titanium microplates, Titanium network, fascia or silicon material. Chemotherapy has only been administered in cases of distant metastases or local tumour recurrence.

CONCLUSIVE REMARKS
The fireside conference ended with a question from professor O. Elbrønd, Denmark concerning preventive efforts. It was stressed that nickel and wood dust are welknown etiological factors and it also seems likely that chronic sinusitis plays an important role. Formaldehyde has so far not been shown to cause malignant nasal tumours in man in contrast to the results from rats in whom such exposure causes a high incidence of nasal malignant tumours.

CHAIRMAN: I.S. MACKAY FRCS, LONDON U.K.
CO-CHAIRMAN: A.R. BHIDE, PUNE, INDIA

1. CORRECTION OF THE NASAL PYRAMID

V.P. SOOD, NEW DELHI, INDIA

One of the earliest reports of rhinoplasty was the total reconstruction of the nose using a forehead flap. This was developed in India and later spread worldwide. Interest in rhinoplastic procedures has continued in India and annual courses in this subject have been held for the last fifteen years.

The nasal pyramid constitutes an important component of the nose and deformities in this region include saddle deformities, a prominent dorsal hump, the twisted nose and a broad dorsum. Reducing the naso-labial angle by rotation of the lower lateral cartilages and shortening of the columella is only performed to a limited extent as Indian women prefer an angle of less than 110 degrees.

One of the commonest deformities is the saddle deformity associated with traumatic, iatrogenic and pathological factors, although the introduction of septoplasty in place of submucosal resection has reduced the incidence. The author favours the use of iliac crest graft for large defects and autologous septal or auricular cartilage for the correction of small deformities.

In correcting a prominent dorsal hump, care should be taken to leave the dorsum reasonably high in males although a small dip, particularly in the supratip region is preferred for women. The osteocartilaginous hump being removed en block with a number 15 blade followed by an osteotome, the open roof thus created, is reduced by performing curved lateral osteotomies and in fracture of the nasal bones.

The twisted nose, whether this be developmental or traumatic, presents a surgical challenge. Correction of this deformity involves correction of the septum which the author feels should be undertaken as a single-staged procedure.

Correction of any tip deformities should be undertaken by modification of the lower lateral cartilages. Whether this be undertaken prior to, or after correction of the dorsum, is unimportant provided the tip is remodelled in harmony with the nasal pyramid.

In the discussion which followed this paper, the topic which caused the most controversy was the correction of the twisted nose and in particular, whether this should be undertaken as a one-stage or two-staged procedure. Some participants felt that the best method was a single-staged operation in which the septum, upper laterals and bony parts of the nose were repositioned to the midline and that the first operation was the best opportunity to correct this as scar tissue would make any further procedure more difficult.

A contrasting view was held by others who felt that in the presence of severe deviation of the septum, radical surgery may destabilise the structures such that the desired profile might be difficult to achieve and that in this situation, a radical septoplasty and repositioning of the upper laterals and nasal bones should be performed as a primary procedure followed by correction of any profile deformity and modification of the tip as a secondary procedure.

2. AUGMENTATION RHINOPLASTY

M. OSADA, R. TANINO, M. NISHIMURA, KANAGAWA, JAPAN

Augmentation rhinoplasty is the commonest rhinoplastic procedure undertaken in Orientals. This operation has been performed since the last century. In the early days, Ivory was used although this produced a hard and unnatural-looking nose and was later replaced by paraffin which, although softer, resulted in many serious complications including paraffinomas.

Following World War II, "Organon", a dubious substance of unknown constituents was used by unqualified surgeons and this, too, resulted in various complications including "siliconoma". Over the last few decades, solid silicone, either carved from a block or preformed silicone prostheses have been used in addition to cartilage, bone, fascia and dermis.

The difference between Oriental and Western profiles were described, the former having a less-developed supra-orbital ridge, flatter nasal root, more acute nasolabial angle with less well-developed lower lateral cartilages, short columella and relatively less developed lower jaw. Many measurements have been taken to compare these dimensions but from a practical point of view, have little place in profile planning as "beauty cannot be measured with calipers". It is important, however, to maintain the balance between forehead, maxilla and the lower third of the face with nose occupying the middle third.

The advantages and disadvantages of various graft materials were discussed. The advantages of silastic are that there is no donor site, the prosthesis will not change shape, it is easy to handle and may give a more natural profile. The

disadvantages include: foreign body reaction, mobility of the prosthesis and the need to either carve it from block or have many preformed prostheses available which may be "boat-shaped", "I-type", "L-type" or "super-L-type", the last being more bulbous where it will sit on the anterior nasal spine. Some authors prefer to have a perforated or a prostheses with multiple slits, on the basis that these would be better anchored to soft tissue. However, this may have little advantage and can result in being more difficult to remove should this be necessary.

The preferred incision site is a rim incision, which should be performed bilaterally and as far from the prosthesis as possible. Complications may and do arise and these include: haematoma, infection, malposition, excessive mobility, ridges, over or under augmentation, a "hard" nose, skin discolouration, skin perforation and extrusion. The overall rate of complications is difficult to assess but it is felt to be small enough for this proccedure to continue to be carried out in large numbers.

As the second and third papers both dealt with augmentation, discussion on this paper was deferred, so that both presentations could be discussed together.

3. ARTIFICIAL MATERIALS FOR COSMETIC SURGERY

P. ILLUM, AARHUS, DENMARK

There is a common need for material for augmentation of the nasal septum or to correct the external appearance of the nose. Septal cartilage, if this is available, is the preferred choice but if there is insufficient, two types of material are available:

1. "biologic" referred to as 'grafts' or
2. "synthetic" or alloplastic materials called 'implants'.

In reviewing the historical backgroud, it was interesting to note the success which ivory enjoyed for many years. It could be precisely sculptured into very delicate shapes. Some resorption and occasional fractures or extrusion could occur but many reports revealed favourable results with more than thirty-years follow up. Its use is not advocated today. Other materials include paraffin, silver, gold, platinum, vitallium, cork and guttapercha.

The ideal implant should have:

1. good supportive properties
2. suitable density
3. ease of sculpturing
4. limited tissue reaction
5. no resorption
6. should not migrate or distort
7. there should be a low infection and extrusion rate
8. can be removed with ease, if necessary

The advantage of implants are that there is no risk of contamination with AIDS or hepatitis and unlimited amounts of material are available. The latter problem has resulted in the need for full donor testing and registration of both donor and recipient which has made the use of homologous cartilage is impractical.

The quantity of septal cartilage is limited and it may be necessary to look elsewhere. Auricular cartilage is a good "filler" but less satisfactory where support is required. Rib cartilage and iliac crest provide large amounts of material but may be associated with a painful donor site.

The nose, as recipient site, is associated with particular problems. Unlike the chin, it is not possible to bury the prosthesis deep beneath the soft tissue. The nose is a prominent site and is subject to constant "micro-traumas" and an increased risk of infection.

Although silicone has been used for forty years, the rate of infection and extrusion is high. It is the opinion of the author that: "In time, almost all of the implants come out and silicone is now obsolete in the nose".

Silicone fluid and subdermal injections of teflon do give satisfactory results for the correction of minor deformities. Supramid or Mersilene can be used as a spare filler but give no support and may be difficult to remove. Proplast has excellent supportive properties and is easy to sculpture.

Hydroxyapatite is hard but porous, allowing surrounding soft tissue to invade the surface which anchors the prosthesis firmly. It is highly inert and resistant to infection. In block form, it is so hard that it is difficult to carve but it is available as "gravel" and as such it can be injected with tissue glue to make an excellent "filler".

The second and third papers were then discussed togther. Dr. Bu from the People's Republic of China informed us that Wood in the form of "fresh green willow" had been used in China in the past, apparently with excellent results. It appears that this wood can become calcified and some patients had been successfully followed up for many years.

There was considerable discussion as to the merits and disadvantages of silastic. Many of the doctors treating Oriental patients had considerable experience of large numbers of patients in whom silastic had been used successfully to augment the nose. Although it was accepted that complications can occur, the rate of this was felt to be such that its continued use was justified. The Western participants had very much less experience in this field but generally did not favour its use except in special circumstances such as augmentation for saddle deformity following conditions such as relapsing perichondritis where it might be considered as a single quick method of augmentation which could be undertaken under local anaesthesia and where the implant would not risk alteration in shape by involvement in the disease.

It was generally agreed that prothetic materials had many possible advantages such as lack of a painful donor site, available in unlimited quantaties, should not alter in shape, no risk of contamination by hepatitis or AIDS, could be fashioned into any desired shape and generally made augmentation a relatively short and simple procedure which could very often be undertaken under local anaesthetic. However, it was agreed, that to date, the perfect graft material has not as yet been identified.

FIRESIDE CONFERENCE 10 RADICAL SINUS SURGERY - NEW TREND

Chairmen : WAYOFF M.R.[2], BU G..[3]
Participants : LUND V.[4], JAHNKE V.[5]

[1]Fire-side Conference - Wednesday - Sept. 25.
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M. WAYOFF introduces the speakers and makes some comments about the signification of the word "radical" in sinus surgery. Theorically speaking a radical procedure is untertaken on purpose to cure permanently a given pathological situation, without iatrogeny and with minimal accepted sequelae. Such goals are note easily achieved in some cases of inflammatory pathological changes of the sinus mucosa, where systemic anomalies of the mucosal defense mechanisms are involved, or when the naso-frontal duct is severely obstructed. He wonders that so many large series are published at too short-term, without differentiate the many etiological factors. Most of the recent publications are dealing much more with low rates of complications than with the results concerning the pre-existing pathology. From an other standpoint, it would be outlined that a radical procedure. 1) may be functional, as well as the so-called functional surgery may be radical (or even iatrogenic). 2) is impracticable in the anatomical sense, even on the frontal sinus where obliteration technics are to be used in very selected cases only. Practically speaking, it is not convenient to act functional and radical sinus surgery in opposition. It seems more realistic to withstand the transnasal and the external approaches (including the transantral as well as the transcutaneous routes). As the endoscope is only a tool, all the endoscopically done procedures are not consistently functional, but the

endoscope can be combined with the microscope during the external procedures. One more question is to be discussed here : "is there a place to day for external approaches in sinusitis surgery ?".

G. BU reported that in spite of the development of new equipments (endoscopes, video, adapted succion and forceps), the incidence or complications in ethmoidectomy remains a dark spot. He quotes the impressive publications, by A. MANIGLIA, of severe, major and even fatal complications. These hazards may be prevented - by surgeon's training on cadavers - good understanding of anatomical landmarks - pre-op. CT-scan - never drape the eyes - to look and palpate the eye-ball in view to control any transmitted movement along the lateral wall or to avoid the development of an intra-orbital hematoma. G. BU said that the ethmoïdal labyrinth is occasionally small and poorly pneumatized in oriental persons, and are at risk with overzealous manipulations for a "complete ethmoidectomy". Generaly speaking, the intranasal (I.N.) ethmoidectomy demonstrates a higher incidence of major complications than the (T.A.) trans-antral (De Lima's technic). WANG (1985) reported 2,2 % complications in 1460 cases in I.N. ethmoïdectomies versus 1,07 % according to JIANG'S (1988) in 183 T.A. ethmoidectomies.

V.J. LUND explains that external approach (E.A.) for ethmoidectomy was developed as a reaction with the dangers of I.N. procedures, remembering that MOSHER said : "Endonasal ethmoidectomy was the most blindest and dangerous operation available". LYNCH and PATTERSON are classically known for describing two different E.A. technics, the indications of which are : *chronic infection unresponsive to conservative medication, *complications of acute fronto-ethmoiditis, *recurrent polyposis, *fronto-ethmoidal mucoceles, *access to ant. and post. ethmoidal arteries, *dacryo-cysto-rhinostomy, * repair of C.S.F. leak.

To day, many of these conditions could be done endoscopicaly, and, it would seem an appropriate moment to critically examine the advantages and disadvantages of external approach, in her personal series of 320 patients. The advantages are evident in complicated pathologies with intracranial complications. In recurrent polyps, E.A. ethmoidectomy offers a longer symptoms-free interval. Dural exposure, either surgical or pathological, is easily seen and repaired. None occured in the series of V.J. LUND. It would be outlined that, when dealing with pathologies which may take up to 20 years to develop or to recur, we do have large numbers and long-term follow-up before we can compare the results of the various approaches. Only 6 % of the patients undergoing E.A. were troubled by a webbing scar and less than 1% by naso-lacrimal damage. More significant diplopia can result following E.A., which can be orthoptically corrected or, better surgically prevented by reattaching the trochlea. Failure to maintain or to restore the patency of the frontal recess remains a difficult problem whereas the technic employed, and the combination of E.A. and endonasal endoscopic maneuvers can give the best way for a physiological solution, particularly in mucoceles. As conclusion, the external, or traditional, approach continues to have a place in our armentarium of sinus operations.

V. JAHNKE states that the radical procedures on frontal sinus are to be aware with functions of aeration and drainage. Until now, depending of imaging diagnosis, fronto-ethmoidal mucoceles are treated by E.A. in vast majority of cases. Recurrent sinusitis with or without polyps are to be treated by E.A. when endonasal procedures had not been successfull. There also less frequent indications as trauma with disruption of the posterior wall, osteoma, osteomyelitis, as well as intracranial complications. Surgically speaking, the frontal sinus cannot be separated of the ethmoid, which would be worked at the same time. In most cases, the best choice is the

RITTER-JANSEN or LYNCH operation with resection of the anterior part of the floor of the frontal sinus with external ethmoidectomy. The UFFENORDE mucosal plasty, maintained with a plastic tube for three weeks to prevent stenosis is a very good complement in this procedure. The endoscopic follow-up is also important to clean the drainage area.
V. JAHNKE recommands the removal of the interfrontal septum to offer another route of drainage. The complications of E.A. of the frontal sinus are very rare. The osteoplastic flap operation is suitable when the ethmoid is not interested by the pathology, particularly in trauma cases. In fact, paranasal sinus pathology is often characterized by very unique or peculiar cases, requiring adaptative radical technics, including neurosurgical and/or ophtalmological aspects. Though there is some controversy bethween E.A. and I.A., V. JAHNKE considers that, in many cases, the external technics for frontal sinus are safe and efficient with few complications.

To introduce the discussion, M. WAYOFF stressed that "radicalness" is much more evaluated by the results than by the preoperative planning of the surgeon, and that is particularly true about sinus surgery, that could be also heavily iatrogenic. Unfortunately, G. STROTHERS was unable to give his lecture about the "state of the art" in Caldwell-Luc operation, which seems so discredited to-day. In fact, there is always some indications for the trans-antral approach but, to-day, it will be done microscopicaly, with an endonasal complement; inferior meatotomy is to be avoided but middle meatotomy is mandatory. It was the great merit of De Lima (Brazil) to describe the T.A. route to the ethmoid labyrinth, that may be renewed with endoscopic tools and I.A. combination.

S. KALUSKAR (U.K.) underlines that he is an enthusiastic "endoscopist" and that, in difficult cases, he combined with an E.A. ethmoidectomy.

W. HOSEMANN (Germany) said that he is able to remove all the mucosa of the maxillary sinus by I.A.. He reports also a 51 cases series of papilloma, 45 of which were treated endonasaly.

M. TOS (Danemark) makes some pragmatic remarks about the versatile criterias of reversibility of mucosal changes. Some pathological conditions did not disappear even after functional surgery, particularly in lesions of dental origin, which are largely understimated, and for which up-to-date modifications of the Caldwell Luc operation principles seem to be more efficient.

M. WAYOFF sets another example with the polyps in aspirine intolerance triad, a syndrom with a life-long evolution, where repeated insufficient surgical treatements are routinely noted in the patient history. It seems more convenient to prefer medical treatment in the early stage, and to use radical surgery if necessary : that is to say complete ethmoido-sphenoidectomy for WIEGAND or sinus nasalization for WAYOFF. Such patients may be worsened by half-measured, insufficient and repeated procedures.
Some discussions raised about nasal polyps in cystic fibrosis, the degloving technic approach, and management of trauma. With an audience of about 40 participants, the topic of this fire-side conference faces different pathologies and patients populations.
In such way, it can be concluded that radicalness has different aspects depending of etiological factors.

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INTRODUCTION

The commom cold syndrome is caused by a variety of respiratory viruses. Rhinovirus is the major cause of colds in adults; other viruses which cause colds include coronavirus, respiratory syncytial virus, parainfluenza and influenza virus, adenovirus, herpesvirus and coxsakievirus (7).

It has long been accepted that the symptoms of common colds were caused by destruction of the nasal epithelium by virus and that this epithelial damage sometimes led to secondary bacterial infection resulting in purulent secretions. However, the data to support this concept are limited.

THE HISTOPATHOLOGY OF COLDS.

Recently we have examined the effect of viral infection on the nasal mucosa in patients with naturally acquired cold (etiologic virus unknown), in volunteers with experimental rhinovirus colds, and in an in-vitro model utilizing nasal mucosa.

Biopsies from the inferior turbinate of volunteers with naturally acquired colds were examined at day 2 during illness and at day 14 as a control when the patients were no longer symptomatic (11). Ten representative photos from 26 biopsies were taken with a scanning electron microscope and evaluated under code. The continuity of the epithelium was remarkable (Fig 1); epithelial cells were seen only occasional seen in the mucus. Biopsies obtained on day 2 from each volunteer were not different from those obtained on day 14. Thirty biopsies from patients along with eleven biopsies from normal subjects were examined by light microscopy. No destruction of the epithelium was seen, but the number of neutrophils in the epithelium and lamina propria during illness (day 2) was increased compared to following illness (day 14) and normal controls ($p<0.01$) (Fig 2). Varying degrees of epithelial destruction has been shown by others (1,5,9); the differences may be due to different viruses.

The aerobic bacterial flora of the inferior turbinate (29 patients) and of the nasopharynx (26 patients) has been examined several times during naturally acquired colds (up to day 8) and then for the two months following illness (12). Although one half of the patients reported purulent

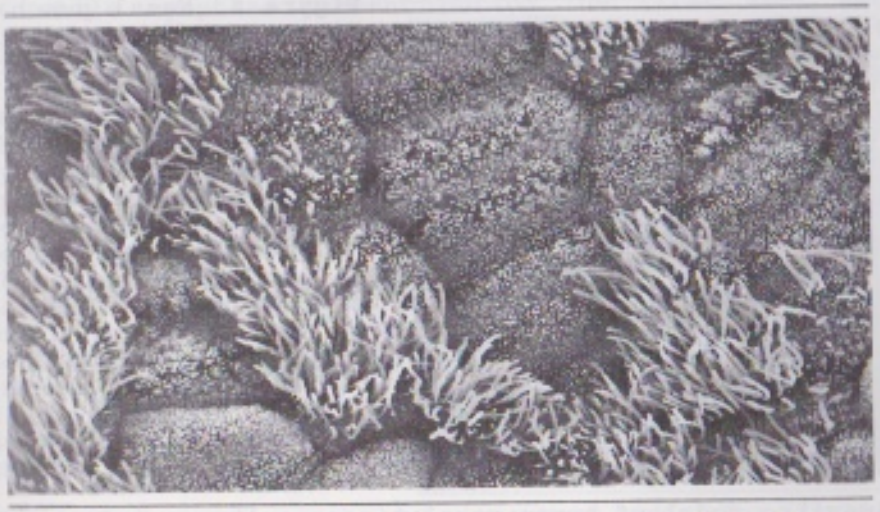

Figure 1. Example of nasal surface during naturally acquired common cold (day 2).

nasal discharge, no change in the aerobic bacterial flora was found during uncomplicated colds.

Histopathology of rhinovirus colds was studied in an experimental viral challenge model. Biopsies from the inferior turbinate of 20 volunteers inoculated with rhinovirus and from 10 sham inoculated volunteers were examined (13). Light microscopy revealed no detectable morphologic abnormalities in the epithelium of infected volunteers when compared to the sham inoculated controls. The number of neutrophils in the epithelium rose significantly above baseline values during the first and second day after inoculation in infected volunteers when compared to non-infected subjects ($p<0.05$). The lack of epithelial destruction during rhinovirus infection has been reported by other workers (2,10).

Lymphocyte subpopulations in the nasal mucosa were examined by immunohistochemical staining technique in 40 volunteers without nasal symptoms and in 20 volunteers inoculated with rhinovirus (16,17). Biopsies from the inferior turbinate of normal volunteers showed a mild lymphocytic infiltration with a predominance of T-lymphocytes over B-lymphocytes. T-helper cells accumulated in the subepithelial area whereas T-suppressor cells had a more even distribution in the lamina propria. Biopsies from the inferior turbinate obtained at day 3 or 5 during rhinovirus infection and on day 14 following illness showed a mild infiltration of lymphocytes similar to the normal nose. No change in the lymphocyte subpopulations occurred during the course of the cold.

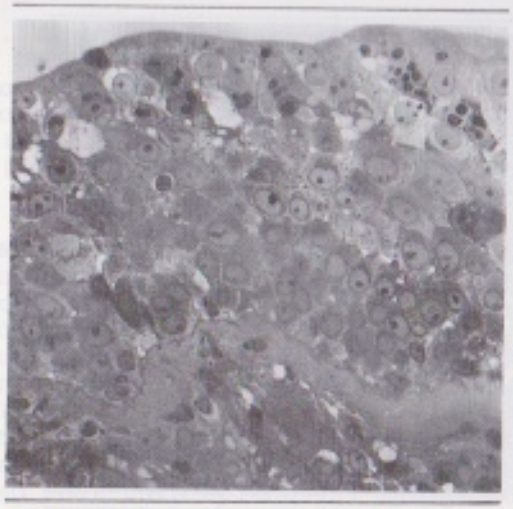

Figure 2. Nasal punch biopsy obtained at day 2 following naturally acquired common cold showing neutrophil infiltration in the surface epithelium.

An in-vitro model of human nasal tissue cultures infected with viruses provided another method for deriving information on the pathogenesis of viral infection in the nose (15). Monolayer cultures of nasal mucosa (polyps, turbinate and adenoid) from 74 patients were established by placing small fragtments in plastic dishes with growth medium. A confluent monolayer of cuboidal and ciliated cells surrounded the fragments within a week. The cultures were exposed to rhinovirus, coronavirus, adenovirus or influenza type A for three hours before unattached virus was removed by washing. An aliquot of media was removed daily from the infected cultures for virus titration. The titer of rhinovirus in the nasal cultures rose after 24 hours to a level above the inoculation dose. Rhinovirus and coronavirus did not produce any detectable cytopathic effect in the nasal epithelial monolayer, whereas adenovirus and influenza virus produced marked changes in the epithelial monolayer. This is in agreement with previous reports (3,6).

LOCATION OF RHINOVIRUS IN THE UPPER AIRWAY DURING COLDS.

Rhinovirus could infect the entire upper airway mucosa or infection could be limited to circumscribed areas. In order to determine the location of viral replication in the nose, a minute volume of rhinovirus suspension was inoculated into the nose by way of the right tear duct in 26 volunteers (14).

Rhinovirus replication was traced by obtaining brush biopsies each day following inoculation from the anterior and posterior part of both the inferior turbinates and the posterior nasopharyngeal wall. Rhinovirus was recovered from the nasopharynx earlier, more frequently and longer than from the nasal cavities; shedding from the nasal cativity was spotty. No virus was recovered by day 21, but the rate of virus recovery did not decline until after day 16 while symptoms present during the first week were diminished or gone during the second week after inoculation.

SUMMARY

The accepted concept that cold symptoms are usually caused by destruction of the nasal epithelium by virus and that epithelial damage may led to secondary bacterial infection is not supported by this work. Although influenza and adenovirus may destroy the epithelium, no destruction of the nasal epithelium was detected either in vivo during natural or rhinovirus cold or in-vitro in nasal epithelial organ cultures. Infiltration of the nasal mucosa with neutrophils early in the cold does not indicate bacterial infection but may be a direct result of the viral infection. Purulent nasal secretions, which are common in uncomplicated colds, were not accompanied by discernible changes in the aerobic bacterial flora.

The nasopharynx may be an important area for further exploration in the study of the pathogenesis of rhinovirus infection since it is a site to which mucus containing virus from the entire nasal mucosa is brought. A prominant feature of the posterior nasopharyngeal wall in both children and adults is a mass of mucosa-associated lymphoid tissue (adenoid or nasopharyngeal tonsils). Preliminary data has suggested that the epithelium overlying the lymphoid tissue expreses ICAM-1 receptors in the normal state, whereas the nasal epithelium does not. This is interesting since the majority of rhinovirus serotypes gain entrance to human cells by this receptor. Symptoms in a rhinovirus cold could result from release of inflammatory and /or neuromediators from the adenoid. Recently, Naclerio et al (8) have demonstrated that kinins and an increased number of neutrophils in nasal secretions correlate with occurrence of symptoms in volunteers with rhinovirus colds.

SYMPTOMATIC AND ANTIVIRAL THERAPY IN THE FUTURE

The lack of destruction of the nasal epithelium during rhinovirus colds has led to a new hypothesis of how symptoms may be produced. Symptoms may occur as a result of a cascade of inflammatory events caused by the viral infection(4,10) rather than being caused by epithelial damage. This is important for designing rational therapy directed at symptoms in the future. The nasopharynx would be an important target for topical antiviral therapy.

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Chairperson: NG Toremalm, Sweden
Co-chairperson: M Ohyama, Japan

Speakers:
T. Deitmer, Germany
Y. Ohashi, Japan
M. Rautiainen, Finland

NG TOREMALM
The mucociliary function belongs to the most basic mechanisms for transportation and defence throughout the entire animal world. For human beings this function has been of increasing interest for diagnostic purposes in our daily clinical work during the last three decades. It has also been the object of extensive experimental investigations all over the world. The influence on the mucociliary function by environmental temperature and humidity changes, air pollutants, bacterial- and viral toxins, pharmaca etc. demands reliable and reproduceable test methods as well as complementary morphological studies.

The aim of this Fireside conference has been to bring about an exchange of informations regarding the advantages and disadvantages of available test methods and procedures and how they can be optimally used for clinical screening and far-reaching experimental studies on humans and animals. Of special interest is the usefulness of mucociliary transport studies compared to local ciliary activities, suitable criteria for laboratory work and selection of tracer substances. The principal methods are briefly shown in Fig. 1. and its headlines are supposed to be a directorial list for our discussions after the three introductory reviews.

T DEITMER
Pathophysiology of the mucociliary system.

To sum up the basics, we all know that the function of mucociliary transport is dependent on normal function of cilia, on enough ciliated surface and on a deliberately balanced two layer system of mucus, containing the periciliary sol and the overlying gel phase, working like a conveyer belt.

1. The measurement of mucus transport in vivo for instance by saccarine, dye or techneticum tests is a good maker for the overall efficacy of mucociliary transport. The problem is that the method seems not to be very precise and is also dependent on the patients cooperation.

2. Watching mucociliary transport on explanted mucosal strips gives the same parameters yet without possible interactions at higher levels, for instance nervous regulations.
3. To measure the frequency of reflections of mucosal waves on an explanted mucosa gives highly accurate values but it is often neglected that this frequency does not only display the activity of the ciliated cells but is as well influenced by the viscoelasticity of the covering mucosa.
4. To perform those measurements of light reflections in vivo gives you the chance to assess higher regulatory effects and apply test solutions not only on the surface but also systemically.
5. To measure ciliary beat frequency from viable nasal smears can be done precisely in order to watch real in vivo reactions.
6. The best method for instant basic pharmacological tests is to expose ciliated cells in vitro and watch changing of the ciliary beat frequency indirectly via the surface light reflections.
With this comments in mind is it often possible to solve discrepancies between studies on the same topic with various applications of the above mentioned methods.

The speaker gave also a survey of the actual literature regarding mucociliary physiology and pathophysiology.

Y OHASHI
The testing for ciliary activity and mucociliary transport.

The mucociliary system is one of the most important defence mechanisms against inhaled or invaded particles including dust, irritant gases, bacteria, viruses and allergens. Disruption of this function may lead to the development of respiratory diseases. Two major techniques are theoretically available for testing of the ciliary activity. The mucociliary transport velocity constitutes a good index of the total mucociliary system but it is also necessary to obtain information about the ciliary activity per se. Therefore, assessment of ciliary activity as well as mucociliary transport may be the key to find the individual background of mucociliary dysfunction.
The speaker gave a summary of his studies regarding the development of cilia, ciliary function and transport capacity during the intrauterine development and the first four weeks after delivery in rabbits. There seems to be a difference in maturity of the different parameters during several weeks before full coordination is established. He also gave a review on practical applications of the test methods after exposure to Influenza A toxins.

M RAUTIAINEN
Using of cultured respiratory cells for testing ciliary function

The speaker introduced a technique for ciliary function studies using cultured human respiratory cells together with a differential interference microscope and a high speed video system. In a suspension culture the respiratory cells form small vesicles and the cells maintain their respiratory type morphologically more than 6 months and also preserves the ciliary activity. The culture contains only ciliated cells without contamination of substances released for example from bacteria. It is therefore possible to study the direct effects of chemical and physical factors.
The high speed video takes 200 pictures per second and the ciliary movements can be evaluated from record tapes using lower speed or even still pictures. About 5-20 ciliated cells can be recorded at the same time. With this system is it possible to study: 1. the ciliary beat frequency, 2. the amplitude, 3. the beat direction, 4. the wave form and 5. the coordination. The advantages of this technique are that every cell and all parts of it can be studied separately. Effects of exposure are directly recorded and the culture material is uniform so it can be used for series of experiments.

DISCUSSION
Following the brief outline of different test methods in fig 1 I think we can notice that stroboscopy and high speed photography belongs to the history of mucociliary investigations due to inexactness and low reproductive ability. The photoelectric methods have been continously improved and is now the standard procedure for indirect recording of moving cilia in the sol-gel layer of secretions via surface light reflections. Two main forces are acting. The propulsive ciliary movements and the breaking forces of the fluids. No one in the auditorium had experiences with the use of laser equipments. Neither was there anyone today working with intracellular microelectrodes for electrophysiological studies in combination with surface reflex recordings.

In vitro experiments
To keep the environmental air temperature and the degree of humidity at a standardized level is of great importance for repeated experiments and comparisons with the results of other colleagues. The advantages and disadvantages of using 32 and 37 degrees centrigrade respectively, was intensively discussed and the arguments were related to differences in body temperature and nasal mucosa temperature as well as temperature differences affecting mucus rheology. Both temperatures were accepted

but experimental work at room temperature had no pleader. The humidity should be kept at about 90 per cent.

In vivo tests
They are easily done on animals but mechanical disturbances must be reduced by anaesthetics and unphysiologic fixation of the head or neck. In vivo tests has however, also been made on humans for example from the back wall of the maxillary sinus during Luc-Caldwell operations by Reimer in the Malmoe group. He found that in chronic sinusitis the mucociliary function was only reduced due to increased amounts of sticky secretions. After irrigation with saline solution the ciliary function was mostly normal.
It was evident that many in the auditorium used viable cell material taken from the nasal mucosa with a brush as a diagnostic screening method. The functional status can be judged by the naked eye or recorded and the material can at the same time be prepared for electron microscopy.

Mucociliary transport
The saccarine test is the one which is most commonly used for clinical purposes. It is easy, quick and uncomplicated. Nuutinen reminded of false negative tests due to a wrong placement of the test material and the need for a good cooperation with the patient. A negative test can sometimes be found even among healthy individuals. There seems to be rapid "high ways" as well as slow "local routes" for transport in the nose and it is therefore not possible to test e.g. pharmaca properly by transport methods. Radioactive particles are also used together with rather expensive scanners but in Germany for example there are objections against the use of radioactive particles in the clinical situation. In Finland on the other hand two different isotops have been used for comparative studies of the two nasal cavities. Total clearence of the nose seems to be used very seldom but this is the method of choise for examination of the deeper airways.
Experimentally a lot of tracer substances have been examined but there was no time for closer discussion on this matter.

Relations between ciliary function and ciliary transport tests

The audience agreed that there is no direct correlation between mucociliary function tests and transport tests. Clinically transportation tests should be looked upon as qualitative because they are not suitable for repeated quantitative studies in man. In animals both methods can be used in vivo but during in vitro conditions the transportation rate gives very inconclusive informations.

Summary
This conference has been very valuable and prosperous for the future thanks to the three interesting reviews and a lively and initiated auditorum. There are still much to be done in order to refine the test methods which are available today and also to introduce new test systems aiming to separate the many different factors which are responsible for the mucociliary defence mechanism, which is indispensable for our health. When we meet next time I hope we will hear more about cell culture studies, sol-gel transport capacities, neural regulating mechanisms etc. However, basicly we always need reliable, well verified and standardized test methods and those have also been the aim of this fireside conference. I want to thank my friend and co-chairman professor Ohyama, the speakers and the co-operating audience anxious to give us new informations and hopefully also to learn more about the fascinating ciliary function.

(Participants during the discussion: The chairpersons, the speakers and Herbert Riechelmann, Germany, Adrian Drake-Lee, U.K., Mark Jorissen, Belgium, Juhani Nuutinen, Finland etc.)

Fig. 1.

MUCOCILIARY TESTS

Ciliary movements	Mucociliary transport
Stroboscopy (Gray, 1931)	Ocular observation
High speed photography (Dahlhamn, 1956)	Inorganic and organic tracers
Photoelectric systems (Dahlhamn & Rylander, 1962 Håkansson & Toremalm, 1965)	Radioactive tracers (Wanner, 1977, Proctor, 1982
Laser beam recording	Total clearance (Albert et al., 1967)
Singel cell observation and recording	
Cell culture (Rautiainen, 1991)	
Intra- and extracellular recording (Håkansson & Toremalm, 1966)	

Desiderio PASSALI
Dept. of E.N.T. Univ. of L'Aquila Medical School - Italy

In a clinical study of a patient suffering from olfactory diseas, the so called objective methods are aimed at revealing particular reactions of the organism caused by olfactory stimulation. Some of these methods should be backed up by the collaboration of the patient being examined (so, they should be called semi-objective) who should always breathe quietly in an absolutely natural way, without altering either the rate or intensity of his/her breathing.

The PSYCHO GALVANIC REFLEX (Bytel et al., 1925) which study the electric cutaneous resistance provoked by a neurovegetative reflex which increase sudoral secretion, allows to quantify only the central anosmias because of the inconstance of its results and the difficulty of their codification.

The PSYCO VOLTAIC REFLEX (Manfredi, 1925) proves more reliable than the previous method; it studies the variation in electromotor force of a Voltaic element consisting of electrodes placed on the skin areas rich in sudoriparous glands and makes it possible to obtain values very close to liminar ones.

The OLFATTO PUPILLARY REFLEX (Lonschinger, 1948; Semeria, 1955-1956) analyses any changes in the diameter of the pupil after an olfactory stimulation with the aid of a time set camera or filming myosis and mydriasis with an appropiately adapted telecamera.

CARDIOCIRCULATORY CHANGES, consist in the increase in the frequency of the heart beat (10%) and rise of blood pressure (10%) as responses for a stimulation of olfactory and olfactory-trigeminal substances, are not found for all subjects.

The study of RESPIRATORY REFLEX is especially possible using olfacto-gusto-trigeminal substances. In fact, they are the only ones to guarantee a right response consisting of changes in frequency, rate and amplitude of breathing. Besides, a computerized rhinomanometric study with careful analysis of NASAL RESPIRATORY REFLEX (Montserrat, 1974-1977; Monserrat et al., 1978; Bellussi, 1978) allows the observation of the variation in flow and pressure of breathing in or out of the nose air gradient (increase in frequency, decrease in the same; pauses in breathing, disorganized tracing). Our research unit also study the olfacto-respiratory reflex, measuring and analysing it on the rhinomanometric tracing. The equipment used for this aim consists of a two-channel anterior rhinoreomanometer (Cottle P. F. 2001 model) connected up to a Guerrier-Uziel olfactometer. The rhinomanometer has been modified by the application of a special constructed nasal funnel and provided with a side outlet connected through a rubber plug to the test tube containing the stimulating odours substances and with a small silicon tube linking the olfactometer with the equipment for recording respiratory activity. The siringe in the olfactometer delivers 30 cc of air at a speed of 1.5 cm per second. In this procedure the substanced used are anetol, linolol, hexaltolide, vanilin and thymol. The analyses of the tracing obtained (reduction of frequency, increase of frequency, disorganization of the tracing, respiratory arrest) do not lead to recognition in all cases of a correlation between the type of response and the substance utilised. The investigation of variations in encephalic electric potentials and more generally any changes in the electroencephalographic tracing are possible using OLFACTOENCEPHALOGRAPHY. This examination requires a fairly expansive equipment and it isn't possible to study the responses caused by an olfactory stimulation if any basic electric alterations are present.

At the present time the most complete objective method is the POLYGRAPHIC METOD (Van der Eeckhaut, 1978) which provides simultaneous recording and graphic documentation of contemporaneous variation of different neurovegetative reflex parameters. Neverthless the equipment is somewhat costly and requires ongoing assistance.

The EVOKED OLFACTORY POTENTIALS rapresent ,as showed by Lorenzo Marcucci ,an highly sensible objective method of investigation in patient suffering from olfactory diseas. This method makes it possible to examine cortical electric variations in the projection areas of the centres and olfactory pathways after positioning electrodes in the rhinopharynx or at the top. Neverthless the equipment is not yet standard, the test is extremely costly and difficult to carry out, the result obtained may help the researchers set up a special diagnostic protocol.

A pratical test kit so called T&T OLFACTOMETER was completed in 1975 by Takagi and Toyota. It consist as Furukawa Mitsuru mentioned of five test odors: each set contains eight bottles for each of the four odors (A-B-C-D-E) and seven bottles for Ciclotene (B) for a total of 39 bottles. Starting from the lowest concentrations of each rispective odor, the patient is requested to name or to describe the quality of an odor. The olfactogram is developed to record the results of clinical tests with the T&T OLFACTOMETER. The VENOUS OLFACTORY TEST is also used to detect an olfactory disease. As an odorous chemical, original

sol ution of Alinamina is injected into median vene of the left arm and latent time which is a period between the initiation of injection and occurrence of garlic smell, and duration time which is a period between the occurrence and disapparence of smell are measured. The latent time is influenced by olfactory acuity and duration time depends on olfactory adaptation phenomenon. This test is especially used in Japan to differentiate central olfactory dysfunctions from peripheral ones.

It is well known that the electrical activity of the brain and olfactory epithelium are modified when an odor is sniffed. A great number of investigators studied potentials elicided by odor stimulation. CONTIGENT NEGATIVE VARIATION (CNV) can be a good indicator for objective olfactometry. The principle of this method is the measurement of the voltage change recorder from scalp electrodes. CNV is a negative wave of about 10 microvolts which is produced at the interval between an olfactory stimulation (S1) and a second stimulus (S2) usually a photic or acustical stimulus. The slow potential elicited in the flog olfactory epithelium by application of odorous vapor were named the ELECTRO-OLFACTOGRAM or EOG first by Ottoson. To record human EOG is still a big problem because of technical difficulties concerned with the positioning of the electrodes, odorous stimulation, duration of stimulation time and flow rate, hidden anatomical position of the olfactory epithelium. A tecnique to read the olfactory mucosa has recently been developed by the use of endoscopy. The positive EOG study can help to differentiate anosmia caused by disorders of olfactory epithelium or disorders of central olfactory pathways. At the end of the session Michele Sagnelli has presented an interesting method for objective olfactometry set up by his unity of research group. It is an important contribute to the olfaction Studies.

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Chair: Michael J. Schumacher, Co-Chair: Jan-Ake Wihl

Discussants: Peter Borum, Claus Bachert, Michael J. Schumacher

Dr. Borum began the discussion with an overview of nasal provocation testing (NPT) by summarizing the indications and uses of NPT with histamine, methacholine and allergens. NPT with methacholine was found to be suitable for assessment of non-specific nasal hyperreactivity or for study of effects of medications on nasal reactivity. Allergen challenge may be used to determine nasal sensitivity to particular allergens or to follow seasonal changes in nasal sensitivity. Dr. Bachert discussed recommendations for the safety and reliability of NPT with allergens, methods for allergen challenge and evaluation of nasal responses to allergens. Dr. Schumacher discussed standardization of rhinomanometric measurements, including the differences in approach required for computerized and noncomputerized equipment. The Conference concluded with discussion of the value and frequency of use of NPT in routine clinical practice.

INDICATIONS AND PRACTICAL APPLICATIONS

The most frequent application of NPT is for testing nasal sensitivity to aeroallergens. NPT with allergens may help to resolve discrepancies between the clinical history and skin prick tests or serum IgE antibodies. NPT with allergens may be useful in perennial rhinitis when skin tests with perennially present allergens, e.g., mites or molds, are positive. This could help to make immunotherapy mixtures more relevant, and could establish a basis for environmental control when this could require lifestyle or workplace changes.

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NPT with histamine or methacholine may be useful in identifying non-specific hyperreactivity of the nose. Dr. Borum prefers methacholine challenge to histamine challenge because unphysiologically high doses of histamine are needed to obtain a positive NPT and because histamine causes edema that is not blocked by H1 and H2 antihistamines. The predominant effect of methacholine in NPT is a dose-related stimulation of mucous secretion. NPT of rhinitis patients with methacholine produces hypersecretion at average doses significantly lower than in normal individuals. However, a considerable overlap between normal patients and patients with nonallergic vasomotor rhinitis is found, reducing the value of the test in identifying nonallergic rhinitis in the individual patient. Nonspecific hyperreactivity to methacholine is also found in patients with allergic rhinitis and the test cannot distinguish vasomotor rhinitis from allergic rhinitis. Methacholine challenge can be used to study effects of intranasal steroids and anticholinergic drugs. For example, ipratropium bromide blocks the secretory effects of methacholine and this blocking effect lasts up to eight hours when delivered in a non-aqueous form. Ipratropium bromide is more effective in blocking the effects of methacholine in normal patients than in patients with vasomotor rhinitis.

Other tests for nonspecific nasal reactivity include challenge with cold air or ingestion of spicy food. Both types of challenge may be blocked by anticholinergic agents such as ipratropium. After viral respiratory infections methacholine challenge by NPT is not as useful as methacholine challenge by bronchoprovocation because hyperreactivity to methacholine in the nose persists for only two days as compared with many weeks in the lungs. Methacholine NPT may be used to follow changes in nonspecific hyperreactivity in patients with allergic rhinitis since it has been shown that sensitivity to both methacholine and allergens increases during the pollen season in Europe. Patients with perennial allergic rhinitis tend to have higher sensitivities to methacholine as compared with patients with seasonal allergic rhinitis.

METHODS FOR NPT WITH ALLERGENS

In general, NPT with allergens should be constructed and used with the following considerations: safety, specificity, reproducibility, practicality for daily use, and comparability with natural environmental conditions. Allergen NPT is safe provided that the patient has stable disease. NPT should not be performed if the patient has nasal infection, unstable asthma, or has had nasal surgery within

the past 8-10 weeks. The room in which NPT is to be done must not be contaminated with allergens because of the additive effects on patients tested subsequently. The allergen distribution must be limited to the nose. This can be achieved with the spray technique if the spray is delivered at full inspiration and if the following expiration is transnasal. Complications have been limited to pharyngeal or soft palate edema, occurring after less than 1% of challenges. Nevertheless, emergency supplies must be available and the staff must be trained to treat anaphylaxis.

The sensitivity and specificity of allergen NPT may be influenced by medications taken prior to the test. It is recommended that lyophilized allergens be reconstituted on the day of the test to ensure delivery of a standardized dose. Diluents should be determined to have no effect on the nose. Dr. Bachert and others in the Conference delivered the allergens to only one side of the nose, to reduce the level of symptoms experienced by the patient during a positive test, and for additional safety. However, there was no agreement in the Conference on unilateral vs bilateral nasal challenge. Delivery systems discussed included paper disks, pipettes, nebulizers, spray atomizers, whole pollen grains and allergen challenge chambers. Cotton wool applicators are not recommended because of their irritative effect. A suitable pump spray for NPT could deliver 0.04 ml to be sprayed twice in each side of the nose. In all allergen challenge tests, a baseline period of observation is necessary to be certain that the patient is stable before proceeding with the test. The patient must then be challenged with an allergen-free diluent. If the patient responds significantly to the diluent, the test should be abandoned and rescheduled for a different day. If the patient remains stable after challenge with the diluent, allergen is delivered either as a single dose or in gradually increasing doses to determine the lowest concentration of allergen that provokes a measurable, significant response. The single dose method, widely used in Europe, is most practical for office use, while the threshold technique is more precise. No data was offered at the Conference to validate the single dose method. Allergen NPT every two or three days results in an increase in nasal reactivity to allergen. For this reason, at least one week should elapse between allergen NPT.

RESPONSE MEASUREMENTS

Three types of nasal response were discussed: obstruction, secretion and nasal irritation. Recommended methods for measurement of response to challenge depended on the type of challenge. Methacholine causes a predominantly secretory response, with inconsistent decreases in nasal patency. For this reason, measurement of nasal secretions is more important than rhinomanometry for studying responses to methacholine challenge. For challenge testing with histamine or allergens, hypersecretion, sneezing and changes in nasal patency are all important and must all be measured in a reproducible way. Although measurement of nasal patency by rhinomanometry appears to be the most accurate and precise method, Dr. Borum found that changes in nasal airway resistance were less reproducible than the sneeze count or measurement of volume of nasal secretions. It is impossible to measure total nasal secretion, but changes in amount of nasal secretions can be assessed by weighing the amount of mucus expelled into preweighed paper handkerchiefs. When patients allergic to grass pollen are challenged in the grass pollen season and then rechallenged five months later, there was a decrease in sensitivity of the nose to allergen. Biphasic responses to allergen NPT are not routinely observed in patients with allergic rhinitis. Although there was no difference between the threshold for allergen challenge of patients with isolated immediate reactions to NPT and patients with immediate and late reactions, patients with late phase reactions to NPT tended to have more symptoms during the hay fever season as compared with patients with isolated immediate phase reactions. Therefore, it was recommended that late phase reactions be studied to improve the clinical relevance of allergen NPT.

There was no consensus about how scores for nasal secretions, sneezing and rhinomanometric measurements should be combined. There was also no consensus over whether the nose should be challenged unilaterally or bilaterally or whether rhinomanometry should be performed by the anterior or posterior method. Anterior rhinomanometry is more convenient but may be subject to artifacts due to the nasal cycle during the allergen challenge test. Nasal reactivity to allergens during NPT may be affected by the priming effect of exposure to other allergens in the patient's environment. Therefore, nasal challenge with any allergen could be affected by the season in which the challenge is done. Dr. Horak (Vienna) commented that allergen challenges with a pump spray is quite different from natural exposure to allergens and recommended that the only way to obtain results comparable with the patient's symptom scores from natural exposure is to mimic environmental exposure by using a challenge chamber. This point was conceded but it was clear that his technique could not be applied to routine clinical practice.

RHINOMANOMETRY

Rhinomanometric measurement of nasal patency is the most convenient method to accurately measure nasal obstruction following NPT. Standardization of methods for posterior rhinomanometry were discussed. In this technique, it is essential for visual observation of the pressure/flow curve during performance of the test and to exclude the influence of artifacts on the results. (Visualization of the curve is also useful in computerized anterior rhinomanometry, but is less important because artifacts are uncommon with a carefully applied anterior technique). Small but significant differences in the pressure/flow curve in inspiration and expiration are routinely observed and close examination of the pressure/flow curve at the intersection of the pressure and flow axes (between inspiration and expiration) shows that the curve is actually a loop that almost never passes exactly through the intersection of the axes. This phenomenon, due to a phase shift from a slight delay in flow recordings behind pressure recordings, is of no consequence when resistance is measured by visual inspection of the curve. However, this problem is important for computerized rhinomanometry when resistances are determined near zero flow, where artifactually negative resistances may be computed. Furthermore, a variety of methods for determining nasal resistance from the pressure/flow curve are used by different investigators. To try to resolve these problems with computerized rhinomanometry, a large number of curves (more than 6000) were fitted to the equation

$$R_s = K_1 + K_{2i} \cdot V \text{ if } V \text{ is positive}$$
$$= K_1 - K_{2e} \cdot V \text{ if } V \text{ is negative}$$

The coefficient in determination for curve fitting for every curve was greater than 0.997, suggesting the value of this algorithm from which resistances at any reference point could be derived. For resistance measurements, reference values for flow or pressure are required. Dr. Schumacher agreed with the European recommendations for anterior rhinomanometry: 0.15 kPa (15 mm H_2O) pressure or 0.1 L/sec flow. For posterior rhinomanometry, he suggested 0.05 kPa (5 mm H_2O) pressure or 0.25 L/sec flow.

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with S. Fujita[3], S. Miyazaki[4] and J.H. Park[5]

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Obstructive sleep apnea syndrome is by now quite well-known, and it has been reported that between 2% and 3% of the general population are afflicted with it. In most cases, the syndrome is associated with heavy snoring. The idea that partial obstruction may lead to hypoventilation with desaturation has also been clearly demonstrated. However, recently it has been shown that subjects without decreases in oxygen saturation may also present partial upper airway obstruction, with or without snoring. In spite of the absence of significant impact on blood gases, pathology is demonstrated by the presence of daytime sleepiness (1-3).

Most recently, it has been suggested that upper airway resistance is the major issue. Maximum resistance causes complete closure, but there may be wide variation in resistance. At times it may lead only to short and very transient repetitive alpha EEG arousals. The presence or absence of snoring is irrelevant. In fact, if soft tissues are not elongated, snoring may be non-existent, although upper airway resistance may increase sufficiently to cause repetitive alpha EEG arousals with clinical impact. On the other hand, snoring may be present, particularly if there is a mild nasal obstruction, yet upper airway resistance may not increase sufficiently to lead to clinical symptoms. Interestingly, it appears that women present nearly as often as men some daytime sleepiness without oxygen desaturation. However, women rarely seem to evolve toward maximum upper airway resistance, except in the presence of morbid obesity. Thus there is now a unifying concept concerning changes in upper airway resistance during sleep and their relation to the appearance of clinical symptoms of variable type and severity.

Effort has been made to assess the major site and extent of upper airway compromise during sleep and anatomical

abnormalities in patients with maximal upper airway resistance, i.e. obstructive sleep apnea syndrome. (As of yet there have been no studies of this type with the recently described upper airway resistance syndrome). These investigations have been performed in order to determine the appropriate surgical procedures for certain subjects. The methods used to appreciate these abnormalities involve otorhinolaryngological inspection, which should be performed on a seated a supine subject, with attention to maxillar and mandibular landmarks. A flexible fiberoptic nasopharyngolaryngoscopy must always be associated. Certain maneuvers should be performed during the endoscopic evaluation. However, these maneuvers, particularly the Muller and Valsalva, must be controlled. For example, in the Muller maneuver the subject must be required to reach a specific pressure level, which is measured during the endoscopy. Otherwise, too many individual differences will occur, depending on the effort performed, and very different negative pressure will be obtained during the movement. Thus, no valuable information is provided, because at the extreme, any airway can collapse, and the location of the collapse seen may vary, depending on the degree of effort (2,4). Cephalometric analyses with the subject seated and supine, at end inspiration and end expiration, have been widely used to select patients (5). Computerized tomography, somnofluoroscopy and magnetic resonance imaging may be used only on certain patients selected for their diagnostic difficulties, considering the cost of the procedure. Similarly, dynamic video endoscopy, which uses a water-filled catheter to measure pressure at two different points in the upper airway, a fiberoptic scope, and a custom-fitted nasal mask connected through a pneumotachograph to a servo pressure controller with a positive (nasal CPAP) and a negative pressure source, is a very sophisticated but sleep-disturbing evaluation which usually requires premedication of the subject with a benzodiazepine, which taints the results. Fujita has a classification of upper airway anatomy involvement which delineates whether the problem is located mostly in the oropharynx, the hypopharynx (behind the base of the tongue), or both. Undoubtedly, recognition of the problem is important, as it will guide any therapeutic proposal. One must, however, remember that at times surgery may lead to collapse of the upper airway at a different point: the first location may have served as a "protection" for a collapse at a different place before a palato-pharyngoplasty, for example. Also, the pre-surgical evaluation may not resolve all questions, but this is rare (2,3).

Uvulo-palato-pharyngoplasty (UPPP) is derived from a surgical procedure introduced over 30 years ago by Dr. Ikematsu, the late president of the 3rd International Meeting on Obstructive Sleep Apnea and Chronic Ronchopathy (3). The principle of UPPP is to maximize the potential oropharyngeal airspace without

jeopardizing the physiological function of the soft palate. There have been many techniques used for this procedure, and it is not very difficult to perform. There are, however, known complications which can be minimized by attention to detail and careful limited resection. These complications include bleeding, infection, nasal regurgitation, usually temporary but occasionally long-term, velopharyngeal insufficiency or nasopharyngeal stenosis, and changes in taste or voice tone. UPPP has been associated with other procedures such as nasal surgery and tonsillectomy with or without adenoidectomy. Also, maxillo-mandibular surgery has been performed, particularly by the Stanford team, and lingoplasty has been performed with midline laser glossectomy, particularly by Fujita (2). Surgical techniques for treatment of anatomic obstruction at the hypopharynx include a limited mandibular osteotomy with genioglossus advancement, and the more complex bimaxillary advancement. The rationale for the treatment of the tongue base is that hypopharyngeal obstruction in obstructive sleep apnea is secondary to the position of the tongue base during sleep. A limited mandibular osteotomy does not create more room for the tongue base, but it does place the tongue under tension. This procedure is performed intra-orally. It is most commonly associated with a hyoid myotomy and suspension with fascia lata graft. However, this procedure is performed only if the hyoid bone is located more than 20 mm from the inferior border of the mandible. The bimaxillary advancement is only performed on subjects who have not responded appropriately to other approaches. As the tongue base is an integral part of the mandibular-hyoid complex, any movement of the mandible will affect the posterior airway space. The bimaxillary procedure is well known for treatment of congenital skeletal deformities. It has been modified by maximizing the distance that segments are moved, using outer table calvarial bone grafts with rigid fixation for stabilization and minimal use of intermaxillary fixation (6,7).

Surgical treatment is in strong competition with nasal CPAP (continuous positive airway pressure) (8). Nasal CPAP allows the prevention of tracheostomy in all cases, particularly since the development of different inspiratory and expiratory pressures (BiPap - Respironics, Inc.). The usage of the "pillows" with this equipment may allow elimination of the mask. With the availability of CPAP and BiPap, it is important to be sure that surgery will have good results before submitting any patient to a surgical procedure.

Dental appliances have been tried in different parts of the world. The Esmarch Prosthesis has been used predominantly in Germany. This prosthesis is built individually for each patient by a dental laboratory. It imitates the effect of the Esmarch maneuver and pulls the mandible 3-5 mm forward, opening the

oropharynx by causing an artificial transitory progenia during sleep (9). It seems to give many valid results in patients with mild or moderate obtructive sleep apnea syndrome. However, the results with long-term follow-up polygraphic monitorings are still limited, and polygraphic studies are not available. There are reports of temporo-mandibular joint problems developing after 12 months of continuous usage, but these data are anecdotal, and a large, possibly multi-center study is still awaited.

These treatments should be prepared by behavioral recommendations, particularly elimination of any alcohol intake at least 4 hours before bedtime, in view of the repeated demonstration of the complete elimination of the normal coordination between diaphragm and upper airway dilators. Also, weight loss, cessation of snoring and aggressive treatment of allergies will undoubtedly decrease upper airway resistance. Unfortunately, alcohol and weight reduction programs are not always closely followed by patients.

In summary: we now have a better understanding of the pathophysiology of obstructive sleep apnea and upper airway resistance. However, prediction of the results of surgical treatments is still difficult and requires in-depth investigation of subjects, with testing during sleep.

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INTRODUCTION

Nasopharyngeal carccinoma (NPC) is one of nasopharyngeal cancers which denotes a carcinoma arising from the epithelial cells of the nasopharynx. This definition excludes other nasopharyngeal cancers, such as salivary gland type carcinomas, lymphomas, and sarcomas. Although a rare malignant neoplasm in most countries, NPC occurs, however, in an extraordinarily high frequency among Chinese population (1,2). Using world population in 1976 as the standard population, the age-adjusted annual NPC incidence rate was as high as 8.3 per 100,000 for males and 3.5 per 100,000 for females in Taiwan from 1983 to 1985 (3). The rates in Hong-Kong and Singapore were even more higher than in Taiwan.

PATHOLOGY

Although NPC is an epidermoid cell-lineage carcinoma, a variety of morphologic degrees of differentiation leads to controversy concerning its histologic classification. The WHO (4) recognizes three types: Keratinizing squamous cell carcinoma (WHO-1), nonkeratinizing carcinoma (WHO-2) and undifferentiated carcinoma (WHO-3). The main controversy is the WHO-2 which is generally included in the Micheau classification for undifferentiated carcinoma of nasopharyngeal type (5). The WHO-1 was further divided into classical (WHO-1A), moderately differentiated (WHO-1B) and poorly differentiated carcinomas (WHO-1C). There are quite few of WHO-1A in our experience. NPC in North America was reported to constitute two distinct diseases: WHO-1 in older patients with poor outcome, and WHO-2 or WHO-3 in younger patients with better outcome (6). Neither survival descrepancy nor age difference was found among three WHO's pathological classification in our experience.

EPSTEIN-BARR VIRUS AND NPC

The association of Epstein-Barr virus (EBV) and NPC was first reported in 1966 (7). So far, there are more than 10 types of antibodies against-EBV associated antigens found in NPC patients. Serological mass survey of NPC in Mainland China showed that anti-EBV viral capsid antigen (VCA) in IgA class was a valuable marker for the early detection of NPC (8). Recently, antibody to EBV-specific DNase was also proved to be a marker for the early detection of the disease in Taiwan (9). A prospective study of antibodies to EBV DNase and VCA-IgA for prognostication of NPC patients was carried out in Taiwan. The results showed that anti-DNase antibody titer could be used as a prognostic indicator for local recurrence and subsequent distant metastasis after initial treatment. Anti VCA-IgA antibody titer could be used as a prognostic indicator for subsequent distant metastasis but not for local recurrence (10).

DIAGNOSIS

Diagnosis of NPC is mainly depending upon detailed history taking, physical examination including complete examinations of the head and neck such as cranial nerves, posterior rhinoscopy and/or flexible fiberscopy. Imaging techniques are also helpful. Finally, the diagnosis is made by tissue proof from the nasopharynx by biopsy. CT scan of the nasopharynx

and serum anti EBV-VCA in IgA for diagnosis of NPC are specifically emphasized in this meeting (11).

STAGING

The TNM system of NPC proposed by the American Joint Committee on Cancer and the Union Internationale Contre le Cancer in 1988 is not used neither in Hong-Kong nor in Taiwan, because it is felt that the system is not based upon the natural history of NPC. Our staging system currently used is shown in Table 1.

TABLE 1. Clinical staging of NPC in the National Taiwan University Hospital

Stage	TNM	Remarks
I	T1N0M0	Soft tissues of nasopharynx
II	T2N0M0	Nose, palate, oropharynx, sinus
	T1-2N1*M0	and/or skull base involvement
III	T3N0-1M0	Cranial nerve and/or hypopharynx
	T1-3N2**M0	involvement
IV	T4N0-2M0	Intracranial and/or extensions
	T1-4N2f***M0	beyond the above conditions
	M1	Any distant metastasis

* Above the line of the cricoid prominence.
** At or below the line of the cricoid prominence.
*** As N2 but fixed nodes.

TREATMENT

1. Radiation Therapy

Radiation therapy is the mainstay treatment for this disease. The usual dose schedule is 1.8 to 2 Gy/day, 5 days per week. The usual dose delivered to the primary tumor is 69 to 80 Gy in our institution. Clinically positive lymph node - bearing areas above the clavicle receive at least 60 Gy, and negative necks are treated with 50 Gy for prophylaxis. The tumor is highly radiosensitive in general but its radiocurability is dependent upon tumor volume, delivered dose, and performance status of the patient. The evolution and results of treatment for NPC in our institution is shown in Table 2. With these high dose radiation therapy, the late complications including xerostomia, skin or subcutaneous fibrosis, deafness, trismus, soft tissue necrosis, and osteoradionecrosis etc. caused poor life quality of the surviving NPC patients should not be overemphasized. The use of split-course radiation had been thought to induce cell repopulation during rest period and also with less late toxicity and better tolerance. Thus, we are using split-course radiation in our institution.

Table 2. Five-year survivals of NPC in National Taiwan University Hospital

Period	Methods	5-year survival
1946-1957	250KV X-ray + Radium application	12.0%
1958-1962	Cobalt 60 teletherapy	18.6%
1963-1968	Same as above with a full time radiologist	25.8%
1969-1978	Cobalt 60 + Lineac + Split course	47.8%
1979-1982	Same as above with radiation sensitizer*	70.6%

* Cyclophosphamide, Methotrexate or both (12)

2. Surgery

Though radiation therapy is the primary treatment modality for NPC, local failure is not uncommon. A further dose of external radiation is limited by the tolerance of nearby structures and the management of these patients remains a therapeutic challenge. En bloc resection of the recurrent tumor in the naso-

pharynx was tried in 9 patients with the maxillary swing approach in Hong-Kong. With the median follow-up of 9 months, one patient developed local recurrence. The result was quite statisfactory (13). The maxillary swing approach may offer a chance of eradicating the recurrent or persisted NPC.

3. Chemotherapy

The use of systemic cytotoxics is not a novelty in the management of NPC. Until recently, chemotherapy with BEC (bleomycin, epirubicin, cisplatin) for advanced or recurrent NPC was reported to have excellent results (14), we failed to achieve the same results because of toxicity.

CONCLUSION

NPC is rare in most countries, it is found in a high frequency in Southern Chinese. HLA class I and class II investigations in NPC revealed that A2, B46 and DR9 showed high frequency in Taiwanese NPC (15). Etiologic factors of NPC are not only limited to HLA typing, it is believed to be multiple factors such as hereditary, EBV infection, herb drugs, salted fish, food additives and inhalant carcinogens. EBV serology can be applied for the early detection of NPC. Although radiation therapy is the main treatment for NPC and the results are quite statisfactory. However. the late complications of radiation therapy are very remarkable. To reduce the dosage of radiation therapy to 60 Gy, by adding other modalities of treatment without expense of the final result is expected, thus the quality of life in surviving NPC shall be improved. Concomitant chemotherapy with radiation and immunopotentiation are worthwhile to try and to study in order to achieve this goal.

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INTRODUCTION

Despite the importance of mind in the practice of rhinology, the information on the subject are scanty. The following sentences were taken from the literature :

"The nose deserves more attention from a psychological point of view than is commonly given.The nose, psychologically speaking, is more than a conglomerate of tissues: it constitutes an important part of the Shilder's concept of body image. The correspondence between nose and vagina, with regard to nostrils and wings of the nose,is striking. All kind of sexual conflicts, such as castration-anxiety, latent homosexuality and masturbation can be projected upon the nose because of this correspondence in structure. Various nasal reactions are supposed to be linked with feelings of fear, hostility, guilt and disappointment. Experience shows that any deviation of the nose often has a particular influence on the development of personality structure." (Stokvis, Bolten & van Leeuwaarden, 1963)

"The various adaptive systems of human person, psychological, intrapsychic, nervous, humoral, immunological,etc are interlocked.Severe and personally significant stress distorts selfhood and thus must alter body scheme perceptually and functionally. The nose is an important part of the body-image and the seat of narcissistic investment. Paramount in rhinological intervention is the symbolic meaning of encounter on several levels of psychosexuality in the interaction between doctor and patient. Therefore "cure" or the perseveration of medical activity may be an indication of neurotic need on the part of the patient but also of the doctor." (Gronner, 1963)

"Among the disorders of the nose that are observed to be most intimately related to psychic factors are allergic rhinitis, rhinitis vasomotoria and reflex neurosis. In the treatment of patients with naso-sinusitis consideration should be given to the psychosomatic aspect of the disease."(Takahashi & Saruya, 1971)

"Takahashi considers vasomotor rhinitis as a possible -

consequence of predisposition, stimulation and psychic factors. Berger has described this disorder as a psycho reflective manifestation. Holmes, Goodell and Wolf & Wolf regard this disorder as an active sign of the defensive and protective responses of the nose and experimentally demonstrated it." (Takahashi & Saruya, 1971)
In this fireside conference the subject was presented - and afterwards discussed under three headings : 1. The mind and nose surgery , 2. The mind and nasal symptoms, 3. "Polysurgery" in rhinology.

1. THE MIND AND NOSE SURGERY.
Properly indicated and performed, rhynoseptoplasty removes nasal obstruction and changes to normal the external appearance of the nose, simultaneously improving the self-esteem and self-confidence of the patient. Eventually, such improvements are so important and dramatically changes for better his social behaviour and his own life.
By just changing the shape of a nose a person may look younger. Our unconscious learned - from fairy tales and the classical Hollywood movies - that young people , as well as good people should have a regular nose .On the contrary, the out-laws had an ugly nose. The nose changes in Snow-White's stepmother - as a queen and as a - sorcerer - illustrates it .
Grotesc or just ugly noses can be responsible for nick names that strongly influence the formation of the personality and emotional response pattern of a person.So, in children, such noses should be considered for surgery before they go to the school.
It seems that regular noses are important for a pleasant facial aspect as well as for the development of good social relationships, but eventually - like in the case of other physical handicaps - a conspicuous nose deformity can be compensated by extraordinary intelectual (or other) qualities. Socrates, the phylosopher, for instance, had a very ugly nose...
In some particular cases, a nose deformity can be the "personality" of a face - Jimmy Durant and Barbra Streissand are good examples of it - and the "key" of professional success, personal "charme" or "sex-appeal" .
Some people just don't care about moderate or even big nose defects. On the other hand, minimal problems of - the nasal contour may produce devastating repercussions on the mind - and the libido inclusive - of some others. Attention should be paid before operating on small deformities of the nose, but the correction of such small aesthetical problems may produce amazingly good subjevtive results. These results always depend on the self-esteem and/or self-confidence improvements we can get but, as a gold rule, we cannot forget that, if a nose deformity we are seeing is not proportional to the patient complaints we must consider that a mind problem -even a serious psychopaty - is underlying it.
It is true that in carefully selected cases and the close cooperation of a competent psychiatrist ,neurotic people can be extraordinarily helped by aesthetic or aesthetic/functional surgery of the nose. However, aesthetic - surgery would hardly have a place in the case of psychopaties.
Dramatic changes of a nose shape can be dangerous. Even in cases successfully operated on the emotional repercussion of it can be catastrophic. After such changes ,some patients need prolonged psychiatric treatment as a consequence of loss of identity .
Nose surgeons must be aware that : 1. besides a good function and shape, a nose operated on should be in harmony with the face and personality of the patient ;2. a good subjective result of an aesthetic or aesthetic/functional surgery strongly depends on the emotional attitude of the patient. It means that sometimes a good aesthetic and/or functional result may be a not so good , or even a poor one on the subjective point of view of the patient. So, surgeons should consider the mind of the patient that is asking for nose surgery with so much care as the other items of the pre-operative routine.

2. THE MIND AND NASAL SYMPTOMS (Speaker: H.R. Marcello)*
"Because of different circunstances, the patient suffering from rhinologic symptomatology in fact underestimates it.He does not consult a doctor, not giving the importance of what is happening ; he medicates himself or abides to therapeutic suggestions of his friends,consult neighbours or the chemist."
"Why does he not visit a specialist ? Perhaps because he does not accept his illness . His interpretation is the cause of his diminished sense of power, so a patient - with a good standing of life suffers less from every day

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diseases (...) than a poorer one."
"(...) the poor increases his symptoms expecting by an implicit way to be protected and to establish dependency, while the first does not fall ill. He looks forward to an spontaneous cure or through his possible medication (according to his doctor and doesn't trust him).These are basic psychologic reactions to the disease and take to a somatic , a psychological or organic or physic , and here is where the patient expects the doctor for a solution to his emotional problems with medical or surgical therapy, wich sometimes comes to be obviously unnecessary. This rhinologic patient with emotional disorders insists in his first examination to a tendency to minimize the seriousness of his illness and is not truthful - historically of the symptoms ; and prefer to assume the disorder as recent, considering to be less dangerous. He focalizes the disease so to make it more controlable."
"To classify some of these patients is an specific subject of a psychanalist or a psychiatrist, nevertheless - we know that an hypocondriac is always grieving and anxious because of a misfortune and because of the disease obsession."
"This hypocondriacal illness is present in a variety of signs and rhinosinusal symptoms from the "simple worry", the patient who refers his fear to two or three yearly colds, to the "fixed idea" of a polypus in assimptomatic maxillar, just because it shows in a X-ray,but he thinks it can be something "load" to the "obsession" or real depressive delirium, where the goes through a disturbance of his general cynesthesia, giving place to the apparition of delirius ideas believing himself to be affected by incurable diseases."
"(...) the patient looks forward to a neurosis or any other way to escape from physic conflicts, he tries to avoid a conflictual situation generating tension and - tries to get a reduction of it through the formation of symptoms; symptoms that circunstancially solves the disease."

3. "POLYSURGERY" IN RHINOLOGY (Speaker:Kimitaka Kaga)*
"Polysurgery" refers to an abnormal psychological condition in patients who demand frequent surgeries. They believe that just by surgery they have relieved their symptoms and try to convince the surgeon to operate them on, by exaggerating their complaints, mostly when the surgeon tries to explain that surgery is not the adequate solution for their problems. Underneath these patient's behaviour several kinds and grades of neurosis and psychopaties may be found. When a patient has an underlying psychological abnormality, but surgery is indicated for a legitimate medical reason, this condition is not classified as "polysurgery".
In ORL, "polysurgery" is mainly looked for the relief of rhinological symptoms. Apparently it occurs because: 1. the patient fears that rhinological disease may result in intracranial ones, because the paranasal sinuses are located near the brain; 2. manifestations of - rhinological diseases may interfere in interpersonal relationship (e.g. halithosis); 3. it is believed that - rhinological diseases may impair memory and ability to concentrate; 4. paranasal surgery is known by the patient as effective for relieving many rhinological symptoms; 5. most rhinological symptoms are subjective and the surgeon has no means to be sure if the patient's assertives are true.
Nervous patients are very sensitive even to the slightest naso-sinusal symptoms, magnifying their intensity - and signification. On the other hand, the consciousness of these so magnifyed symptoms increases nervousness in a vicious circle. Nasal obstruction is the main com - plaint in 80 % of the patients suffering from rhinological neurosis.
For "polysurgery" patients, standard psychoterapy or Morita's therapy is recommended. Morita's therapy is a Japanese psychoterapic method based on Zen phylosophy, behaviour therapy and use of traquilizers.

FINAL REMARKS
External nose deformities may disturb the mind, as well as chronic nasal diseases, mainly the ones producing anterior discharge, pain or foetor. Minor or bigger behavioural changes may take place. Neurosis may develop - and even latent psychopaties eventually become symptomatic. Furthermore, the nose may be a target organ for somatization in neurotic and psychotic patients. The basic nose reactions are vasomotor and/or secretory and reflect a neurovegetative disorder (e.g.hypersensitivity).

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INTRODUCTION

The olfactory and respiratory functions of the nose were recognized in the early days of medical history. In Hippocrates writings we can find phrases like `free respiration is to be looked upon as contributing much to the safety of the patient` (Hippocrates).

The functional aspect of the nasal physiology has been poorly understood until the 20th century. Nasal obstruction is considered as an alteration of nasal function and besides causing discomfort, it may lead to deterioration of quality of life. Nasal obstruction is related to changes in nasal mucosa or deformities of the nasal skeleton, or both. Surgeons can correct the bony or cartilaginous deformities and reduce the size of the turbinates to improve the nasal airway. The present review aimed to elucidate on these two aspects.

PATIENT SELECTION

In order to obtain a good result after the functional nasal surgery, it is mandatory to select the patients carefully. The history of onset and progression of nasal obstruction and also the physical findings at inspection of the nose with nasal speculum are very important. They usually give a clue to whether surgical intervention is indicated. Sometimes, inspection with the fiberoptic nasendoscope is important as nasal polyps or neoplasms as a cause of nasal obstruction can be excluded.

Rhinomanometry is the graphic record of the quantitative measurement of nasal flow and pressure. Although physiological fluctuations occur within the nose over short periods of time, active rhinomanometry is an objective test to assess nasal obstruction. It is useful not only for postoperative evaluation of nasal function but also in selection of patients for surgery.

The nasal airway resistance in 100 patients who underwent functional septoplasty was measured with the rhinomanometer before and after the operation. The findings showed that when the nasal airway resistance after decongestant was above 0.4 Pa/cm^3/sec then the chance of improving the nasal airflow by surgery would be higher (Broms). This finding was further supported when the normal nasal airway resistance value was obtained by measurements carried out in individuals with no nasal symptoms (Jesen).

In recent years, acoustic rhinometry was introduced to measure the cross-sectional area within the nasal cavity by means of reflection of acoustic clicks (Lenders). Acoustic rhinometry was able not only to distinguish the various deviations of the normal nasal structures, but also to demonstrate objectively the efficacy of the individual rhinosurgical techniques.

SURGICAL TECHNIQUE

1. Reduction of inferior turbinate (Drumheller)

The inferior turbinate was decongested and anesthetized with topical cocaine on cotton applicators. A Beaver blade was used to incise the mucosa superiorly on the turbinate going from posterior end to anterior aspect. The incision was tapered inferiorly and stopped just where turbinate mucosa met the vestibular skin. A second incision was made parallel to the first and the width of the mucosal strip was the amount of mucosa that was to be removed, usually 4 mm wide. Forceps were used to pick up the anterior aspect of the mucosal strip and it was removed with the blade upto the pyriform aperture. The periosteum over the turbinate bone was elevated and the inferior margin of the bone was located and dissected free from the anterior to posterior aspect. The lateral mucosa was then lifted off the bone which was then isolated. Turbinectomy scissors were used to cut the bone along the superior mucosal incision. Before removing the bone, it should be freed from mucosal attachments, otherwise mucosal tear would be inevitable.

After removal of the bone and mucosa, the mucosal

edges were approximated with 5/0 chromic catgut suture. A loop was placed at the end of the suture and after passing the needle through the posterior limit of the incision, the needle was passed through the loop. The suture was cinched down on the loop and a continuous suture was then run to the anterior limit of the incision and tied. When the mucosal incision was closed, the middle and posterior third of the inferior turinate was out-fractured. An antibiotic soaked nasal pack was inserted and was left in the nasal cavity for 5 days.

2. Funtional septoplasty

This was first introduced by Cottle where the nasal pyramid was lowered without destroying the integrity of the nasal dorsum (Cottle). After resection of a horizontal and vertical strip of cartilaginous and bony components of the nasal septum and lateral osteotomies of the lateral nasal wall, the nasal pyramid could be pushed down. A wedge resection of the bony nasal pyramid helped to restore the functional integrity (Pirsig).

DISCUSSION

With functional nasal surgery, pathologies in the nose is corrected in such a way so as to restore or to improve nasal function. At the time of surgery the nasal mucosa should be handled with as little injury as possible and supporting parts of the nasal passage such as the cartilage and bone should not be removed unnecessarily to avoid formation of nasal deformities. The formation of these deformities may in turn lead to nasal obstruction and increase nasal airway resistance.

The vessels of the lateral nasal wall and the turbinates are shown to run along the long axis of the inferior turinate (Burnham). Incisions on the inferior turbinate placed longitudinally will result in minimal bleeding and disturbance.

The form of the airway has an important bearing on the amount of tissue that needs to be removed. The narrowest part of the nasal airway is at the nasal valve area which includes the anterior part of the inferior turbinate. Physical or chemical destruction of the turbinate mucosa and bone cannot be precisely controlled, while on the other hand surgical removal of the whole inferior turbinate destroys the form of the airway and may lead to excessive crust formation.

Reduction of the inferior turbinate is more critical at the anterior third (House). The surgical technique, as described by Drumheller, gives an excellent account of the method in reducing the inferior turbinate to improve nasal function. The turbinate bone is preserved posteriorly where a significant amount of vessels for the lateral nasal wall course through it. A portion of the anterior turbinate bone is preserved to give support to the reconstructed turbinate. The defect on the turbinate mucosa is closed to minimize damage to the respiratory epithelium and thus affecting mucociliary clearance. The form of the nasal airway is maintained as close to normal as possible. Reduction of the anterior part of the inferior turbinate besides increasing airflow at the nasal valve area, it also allows a better positioning of the septum if a septoplasty is carried out at the same time, especially on the concave side of the nasal septum.

With functional septoplasty, the operating time is longer than the traditional submucous resection of the nasal cartilage. The advantages include better functional results, a lower complication rate and it is possible to reoperate in these noses if required. The push down technique, as described by Cottle, is an elegant and relatively atraumatic procedure but occasionally the lateral osteotomies may lead to unsatisfactory outcome. When combined with the wedge resection of the bony portion of the nasal pyramid, better functional results can be obtained (Pirsig).

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FIRESIDE CONFERENCE 19 WEGENER'S GRANULOMATOSIS AND LETHAL MIDLINE GRANULOMA

Chairperson: E. B. Kern, M.D.
Co-chairperson: T. Ishikawa, M.D.

Panelists: L. H. Weiland, M.D.
N. Rasmussen, M.D.
N. Yamanaka, M.D.
T. J. McDonald, M.D.

What is Wegener's granulomatosis? How is it characterized pathologically? Is lethal midline granuloma a pathological or clinical term? How does polymorphic reticulosis fit into this whole picture of midfacial destructive lesions? How does malignant lymphoma fit in with polymorphic reticulosis? How are each of these conditions separated, classified, and treated? These were the basic questions that were answered during this fireside conference.

First, we should start with the pathology of Wegener's granulomatosis. Actually, Wegener's granulomatosis is an inflammatory disease with a marked predilection for the respiratory tract. Microscopically it is characterized by necrotizing granulomatosis and vasculitis. The etiology of Wegener's granulomatosis is unknown. However, some investigators feel that the initial phase is probably related to an unidentified infectious agent. The granulomas in this disease have microscopic features that include central necrosis with smudgy basophilic material, an irregular serpiginous and stellate morphology, and an outer ring of palisading histiocytes. The vascular lesion is one of inflammation with lymphocytes and histiocytes. Eosinophils are present in variable quantities. Occasionally the vascular lesion includes fibrinous necrosis. Complete obstruction of the inflamed vascular lesion is not uncommon. Multinucleated histiocytic giant cells are present in practically all cases of Wegener's granulomatosis. These giant cells might be present within the granulomas, within the vasculitis or within the intervening tissues. The classical microscopic findings in Wegener's granulomatosis are most readily observed in the pulmonary lesions. In nasal tissues, primarily because the biopsies tend to be small, the classical triad of morphologic findings can be somewhat evasive. Usually, the nasal biopsies show intense chronic inflammation with necrosis, multinucleated giant cells and vasculitis. Granulomas of the size and extent common to the lungs are relatively rare in the upper respiratory tract. In classical Wegener's granulomatosis, systemic involvement is present. Localized or limited forms of the disease also occur. Pathological involvement of the extra-respiratory organs usually show vasculitis. However, the typical necrotizing granulomas are unusual in extra-respiratory locations.

Lethal midline granuloma is a misleading term. It should not be used in a pathological sense since it lacks specificity. It is an acceptable clinical term if used in the context of a nonspecific destructive midfacial lesion. The differential diagnosis of lethal midline granulomas includes neoplasms, primarily malignant lymphoma, specific infections and polymorphic reticulosis. Polymorphic reticulosis, synonymously called lymphomatoid granulomatosis, is now considered (and proven) to be a relatively indolent malignant lymphoma with T-cell identity. Distinction between Wegener's granulomatosis and the T-cell lymphomas that comprise lethal midline granulomas, polymorphic reticulosis and lymphomatoid granulomatosis is important in terms of treatment, prognosis and overall patient management. Since these diseases have overlap characteristics, it is important for physicians, surgeons and pathologists to maintain open communication relative to their findings. In general, the diagnosis of Wegener's granulomatosis should be made only by the attending physician who has available the clinical findings, the results of microbiological cultures, and the report of the pathologist who simply states "consistent with Wegener's granulomatosis."

The pathogenesis of Wegener's granulomatosis is a more complicated story. With the discovery of the strong association between autoantibodies against cytoplasmic constituents of neutrophils and monocytes and active Wegener's granulomatosis, investigations of the pathogenesis of Wegener's granulomatosis have become centered around these antibodies. They are directed against proteinase3 (PR3) and are termed C-ANCA (for Classical/Cytoplasmic Anti-Neutrophil Cytoplasm Antibodies, defined by indirect immunoflourescence).

IgG-C-ANCA increases with increasing disease activity from undetectable levels. They are eventually found in up to 95% of active Wegener's graulomatosis patients. IgM- and IgA-C-ANCA are also detected in 20-30% of active patients. A shift from IgM- to IgG-C-ANCA like the response to foreign (i.e. microbial) antigens has not been observed in Wegener's granulomatosis. A possible primary infectious "flu"-like event, however, may precede the onset of disease by many months.

Stimulation with PR3 of peripheral blood mononuclear cells from untreated, active Wegener's granulomatosis patients induces a T-cell proliferative response which is not seen in treated patients in remission or in healthy persons. The marginally increased frequencies of the MHC antigens HLA-B7, B8, DR2 and DR3 are of uncertain significance. Giant cells and epitheloid cells, both derived from monocytes, are prominent cells in active lesions. These findings could reflect an acquired defect in processing PR3 or homologous antigen, causing activation of T-cells and B-cells specific for PR3.

B-cells from Wegener's granulomatosis patients but not from normals can be stimulated with Epstein-Barr virus to produce IgM-C-ANCA. Peripheral blood mononuclear cells from active, untreated Wegener's granulomatosis patients yield a significantly depressed Ig production after stimulation with Epstein-Barr virus and PWM. Thus, the specific up-regulation of C-ANCA production in Wegener's granulomatosis patients is accompanied by a general down-regulation of B-cell function.

IgG-C-ANCA specifically activates normal TNG-primed neutrophils. The stimulatory effect is exerted by the IgG3 fraction of C-ANCA. This fraction is selectively increased during active disease. Activation of neutrophils may induce neutrophil adhesion to small vessel walls and thereby contribute to vasculitis and glomerulonephritis.

PR3 is a potent protease capable of degrading basal membranes. C-ANCA may interfere with normal binding of PR3 to protease-inhibitors which may lead to localized presence of PR3 in small vessels thereby causing vasculitis and glomerulonephritis.

Despite the rapid unravelling of the possible pathogenetic mechanisms in Wegener's granulomatosis, the etiology and initiating events are still unknown.

Malignant lymphomas of the nose and nasopharynx show marked clinicopathologic, immunologic, and prognostic diversity. Some of them show clinical features consistent with so-called lethal midline granuloma, a clinical term generally used to describe ulcerative and destructive lesions occurring in the upper aerodigestive tract.

The clinicopathologic and immunologic features were studied in 21 cases of nasal malignant lymphomas with a mean age of 50.2 years at initial presentation. Based on tumor growing patterns, they were classified into two major groups, malignant lymphomas of the expanding type (9 cases) and malignant lymphomas of the infiltrative type (12 cases). The malignant lymphomas of the latter type seemed to be compatible with neoplastic counterpart of lethal midline granuloma. Immunophenotypes of tumor cells in each type were as follows: in 9 cases of expanding type of malignant lymphomas, 5 had B-cell phenotypes and 4 had T-cell phenotypes, whereas all 12 cases of the infiltrative type malignant lymphomas had T-cell phenotypes.

Eight cases in infiltrative-type malignant lymphomas which were identified histologically and phenotypically as peripheral T-cell lymphoma were studied with respect to the association of Epstein-Barr virus. Six of 8 cases Epstein-Barr virus DNA was detected in the nasal tumor biopsy specimens by Southern blotting and in-vitro hybridization with simultaneous detection of Epstein-

Barr virus-determined nuclear antigen and T-cell surface markers by two-color immunofluorescence. Further immunofluorescence and Northern blotting revealed that Epstein-Barr virus NA2 gene and also latent membrane protein gene were expressed in the nasal tumor cells. The patients had high serum titers of antibodies to Epstein-Barr virus.

In recent 5 cases of infiltrative-type malignant lymphomas, the genotype of the nasal tumor cells were analysed by Southern blot hybridization. Four of 5 cases showed a discrete rearrangement of the beta-T-cell receptor genes or the gamma-T-cell receptor genes.

These findings strongly suggest that infiltrative-type malignant lymphomas, i.e., so-called lethal midline granuloma, is a clonal T-cell lymphoproliferative disorder causally associated with Epstein-Barr virus.

The clinical aspects of Wegener's granulomatosis and lethal midline granulomas are really interesting. In previous years, terms used to describe patients with destruction of the nose and face were "lethal midline granuloma," "malignant granuloma," "malignant midline reticulosis," and "Stuart's granuloma." Many of these lesions were in fact: (1) true neoplastic process such as squamous cell carcinoma; (2) destructive lesions due to tuberculosis and fungal infections; (3) diseases secondary to metabolic states as in diabetes gangrenescens; (4) true malignant lymphoma; and (5) processes secondary to vasculitis.

Now, with precise histopathologic examination and excellent dialogue between surgeon and pathologist, and more recently with the use of genetic probes, abnormal clonal genetic sequences in the DNA can be identified and more precise terminology can be used. Thus, patients now can be diagnosed as Wegener's granulomatosis whose rhinologic symptoms are characterized by progressive nasal obstruction, bloody rhinorrhea with crusting, vague pain over the nose, and nasal dorsal tenderness. Usually, these patients have mucosal ulceration of the nose, with or without septal perforation. Other areas of the head and neck can be involved, and they include orbital, otologic, oral, and subglottic involvement. Laboratory findings include abnormal sedimentation rate, mild anemia, abnormal urinary sediment, raised serum creatinine, and altered chest radiographs. The ability to demonstrate the activity of serum IgG antibodies against cytoplasmic components of neutrophils (ACPA test) is the latest test that helps in the diagnosis.

The other disease, lethal midline granuloma, is more correctly called polymorphic reticulosis (lymphomatoid granulomatosis). With the help of genetic probes, this is now more correctly understood as T-cell lymphoma.

SUMMARY

In summary, Wegener's granulomatosis is a systemic illness that is characterized pathologically by necrotizing granulomatosis and vasculitis. Lethal midline granuloma is not a pathological term. Lethal midline granuloma is a clinical term, and in reality, lethal midline granuloma has been proven to be polymorphic reticulosis and not Wegener's granulomatosis. Polymorphic reticulosis is now understood to be a T-cell lymphoma. Further study of these malignant lymphomas has shown that these T-cell lymphoproliferative disorders may be causally associated with Epstein-Barr virus. Although there is strong association between autoantibodies against cytoplasmic constituents of neurophils and monocytes in patients with active Wegener's granulomatosis, the exact pathogenic mechanism in Wegener's granulomatosis and the etiology is still unknown. IgG-C-ANAC (C-ANAC stands for Classical/Cytoplasmic Anti-Neutrophil Cytoplastm Antibodies) increases with increasing disease activity from undetectable levels to up to 95% of active Wegener's granulomatosis patients.

Rhinologic symptoms in Wegener's granulomatosis include progressive nasal obstruction, bloody rhinorrhea with crusting, and vague pain and tenderness of the nasal dorsum. Usually these patients have mucosal ulcerations of the nose with or without a septal perforation. Other areas of the head and neck can be involved, and they include orbital, otologic, oral, and subglottic involvement.

Hallmarks of malignant lymphoma (polymorphic reticulosis) when it involves the upper airway include rapid localized destruction of the nose, orbit, paranasal sinuses, and hard palate.

Treatment for Wegener's granulomatosis includes antimicrobial agents in addition to a regimen of cyclophosphamide and glucocorticoids. The treatment for malignant lymphoma (polymorphic reticulosis) is primarily radiation, especially when confined to one site.