downflow patient isolator for strict isolation

Organization for Health Research TNO

The organization of TNO was established by law, under the TNO-Act of October 30th, 1930.
TNO, in Dutch, is the abbreviation of: Toegepast Natuurwetenschappelijk Onderzoek. This means that it is an organization for Applied, Scientific Research. Public Health and preventive medicine are the two most important fields covered by the Organization for Health Research.
This booklet is only meant as an introduction to the subject.

NECESSITY AND POSSIBILITIES OF CONTROLLING THE MICROFLORA IN MAN AND ANIMALS

"THE DESIGN OF A DOWNFLOW PATIENT ISOLATOR"

With the progress made by medicine in the areas of organ transplantation, treatment of cancer, and treatment of extensive burns, the need has increased for a "control" of the microflora in human patients and in experimental animals. In patients with extensive burns for example the barrier represented by the skin, is destroyed. This facilitates the occurrence of infections. In the past few years, a new category of drugs has been developed and is being used in cancer treatment and organ-transplantation. These drugs have an immunosuppressive effect. Immunosuppression of sufficient degree also leads to an increased risk of infections. Both in cancer treatment and organ-transplantation the suppression of the defense capacity is obviously an unwanted side effect. To eliminate infectious complications in these situations and to make optimal use of chemotherapeutic (immunosuppressive) drugs possible, the control of the patients microflora has become a necessity. Knowledge of the basic mechanisms involved in the establishment and continuation of the microflora of man and animals is therefore required.

A good start to the solution of this problem was found with infectious diseases. As the various routes of infection are known in experimental animals, it has become possible to rear them under isolation conditions, adequate to produce and maintain them free of infections. Experimental work has furthermore indicated that there is a close correlation between the **infectiousness** of a certain microorganism (number of cells required to cause an infection) and the **route of infection.** Both give information as to which precautions are required to prevent a contamination that will "take" and cause infection. In mice, for example, it is necessary to supply fresh sterilized drinking water bottles daily to prevent colonization by Pseudomonas aeruginosa (van der Waay et al., 1963). Under conditions of immunosuppression, this becomes a dangerous bacterial pathogen for these animals (as in other animals species and in man). This microorganism multiplies in the drinking water. A drinking bottle can therefore contain millions of cells after a few days at room temperature. If a mouse with a reduced resistance to infection drinks this contaminated water, he will die rapidly from a lethal infection.

For most pathogenic bacteria, however, more complicated precautions are required to prevent contamination with doses that lead to infections. The above mentioned example of pseudomonas in mice was given, because it illustrates that bacterial species exist that often colonize the intestinal tract of healthy human beings and animals without causing any form of infection. However, as soon as the hosts "resistance" is strongly reduced, this microorganism becomes invasive.

Unfortunately it is not only Pseudomonas aeruginosa that gives problems in man and animals with reduced defence capacity. A number of other bacterial species belonging to what is considered the normal endogenous flora, frequently gives rise to the same complications. These microbes are therefore potentially pathogenic (p.p.). In the great majority of cases the digestive tract is then their "portal of entry". This is the reason that our efforts to prevent (or treat) infectious complications in individuals with a strongly decreased resistance, is focussed on the digestive tract.

I. Correlation between bacterial species, colonization resistance, and isolation precautions

Colonization Resistance (C.R.): is the resistance encountered by micro-organisms when they attempt to colonize the digestive tract following oral contamination (van der Waay, 1968, and van der Waay et al., 1970a). The C.R. is defined by that oral dose of bacteria of a certain species that is required to "take" in the digestive tract for a longer period of time (two weeks or more) in 50% of the individuals. The C.R. for a certain bacterial species can obviously differ in different animal species. In mice, evidence has been obtained that for a "14 day take", high oral doses are required of p.p. bacterial species.

Although less information is available about the C.R.-values for various p.p. species in monkeys and man, there is good evidence that this is also the case in primates.

"Degree" of isolation: It will have become clear that it is important to be informed about the C.R. for the various p.p. bacterial species that must be excluded from patients or experimental animals under chemo- or comparable therapy. With this information a proper design of a protective barrier system is much easier. Because of the differences in C.R.-values, the precautions required to prevent colonization and (potentially) an infection, may differ from bacterial species to species and even from animal species to animal

species. Consequently different isolation precautions in different animal species can have the same efficiency.

II. Antibiotic Decontamination

The **elimination of potential pathogens** for the period of reduced resistance to infection, is one of the possibilities in **controlling the microflora.** At present it is possible to eliminate in mice and monkeys, families and genera of bacteria which may cause infections after strong suppression of the defence capacity. These "unwanted species" can (if required) be eliminated more or less selectively from the endogenous flora of the digestive tract. Else, attempts are made to eliminate the entire flora. This "selective" or "complete" decontamination of the digestive tract can be accomplished by employing antibiotics that are not absorbable from the digestive tract, after oral administration. Depending on the antibiotic combination used for **oral antibiotic treatment**, many bacterial species that are "allowed to stay", are as a rule strongly suppressed or eliminated. This implies, however, a strong **reduction of the C.R.** In most sases the C.R. drops to extremely low values for most p.p. species. The consequense of such a strong reduction of the C.R. during oral antibiotic treatment is, that the individual under treatment is colonized following contamniation with a few bacteria that are **resistant to the antibiotic mixture** being supplied for decontamination.

Because in hospitals and also in research labs with experimental animals, antibiotic resistant microorganisms are usually present in the environment, **strict isolation is necessary during Antibiotic Decontamination (A.D.).** Partial isolation certainly reduces the chance of contamination with "resistant bacteria". However, experience to date has shown that **strict isolation** is less laborious and requires less discipline than incomplete isolation and possibly therefore gives better results.

In conclusion: During oral antibiotic supply in individuals with reduced defence capacity, an artificial barrier is required around the patient to "replace" his C.R. for the time that his C.R. is strongly reduced. This is a situation comparable to an artificial kidney that can "replace" the funtion of the patients own kidneys for period of reduced kidney function.

Another important aspect of successful decontamination is the **sterilization of the patients environment during the period of antibiotic supply.** This can only be performed when the patients isolator has **two interconnected chambers.** The individual under treatment can then occupy temporarily one chamber,

appeared also to be the case in pharmaceutical and medical application where absence of living bacterial particles (sterility) is sought.

Handling of patients and animals in a (laminar) flow isolator could be performed with the help of long sterile neoprene gloves. This procedure was first tested with germfree animals (van der Waay and Andreas, 1970).

Because a continuous air stream may **dehydrate** the individual inside, and because the **noise** made by the blower hinders, it was investigated in what manner both factors could be reduced. The solution to this problem was suggested by Cook (1969):

Reduction of the opening through which the air leaves the unit allows for the passage of a smaller volume of air per unit of time and thus leads to a decrease in both dehydration and noise. A 95% reduction of the opening with a flap or plastic drapes (see later) (fig. 1 and 6) made it possible to reduce air volume accordingly. This applies both to laminar flow systems with a horizontally directed flow (cross flow) as to systems with a vertically directed flow (down flow). Obviously closing off of most of the air outlet opening of the device chances the system drastically. It is then (as long as a flap or plastic curtains close the system) not longer a laminar flow system, but an isolator under overpressure.

Based upon experiences with germfree mice (van der Waay and Andreas, 1970) a (laminar) air flow isolator (fig. 1) has been developed for isolation of patients during periods of A.D. and consequently reduced C.R. Such a unit had to meet the following criteria:

1. It has to be easily and rapidly sterilizable (with peracetic fume) without danger to the patient or personnel.
2. Two interconnected chambers were required that could be closed off from each other, so that one chamber could be sterilized while the patient was in the other.
3. An entry lock allowing quick and easy introduction of sterile materials.
4. It has to have a low noise level.
5. In case of emergency direct acces to patient has to be possible, without the necessity of breaking the barrier.
6. A bath tub was required for (daily) skin disinfection (in addition to A.D.).
7. A peracetic acid sterilizable toilet was necessary adepted to the requirements of an absolute bacteriological barrier (fig. 2).

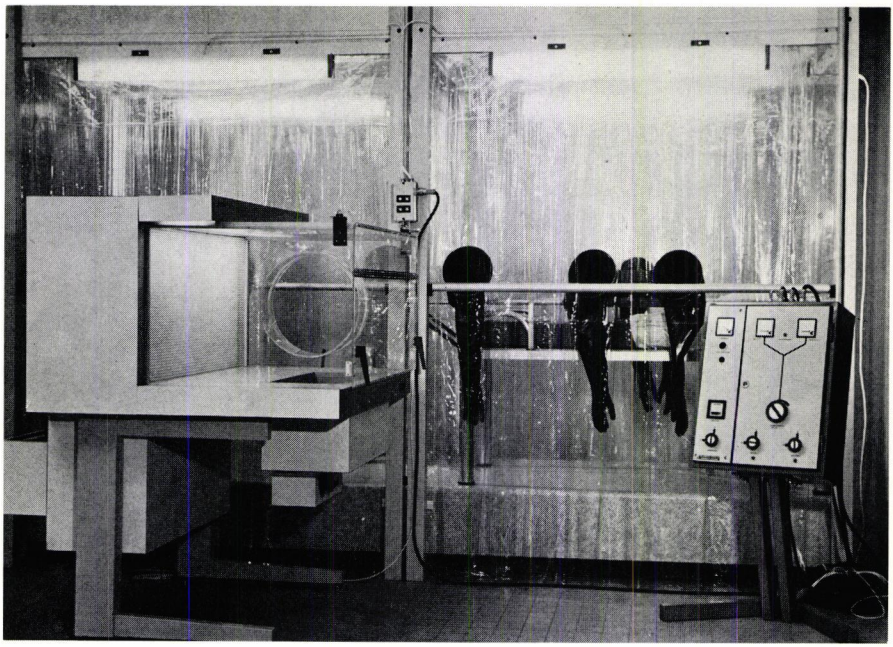
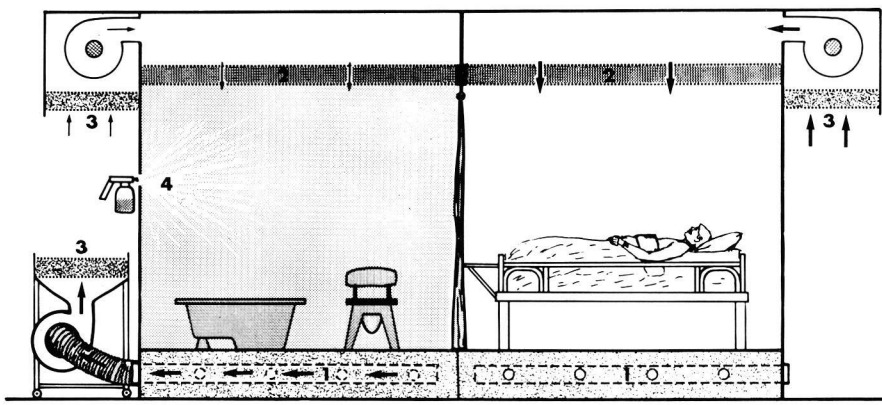


Fig. 1 "Down flow isolator" with two compartiments and a cross flow bench as entry lock for materials.

Fig. 2 Close up of the toilet of the unit.

The introduction of soda lime (pre)filters (fig. 3) made peracetic acid sterilization possible in a hospital environment. Most of the other requirements are obvious. Some have been explained above.

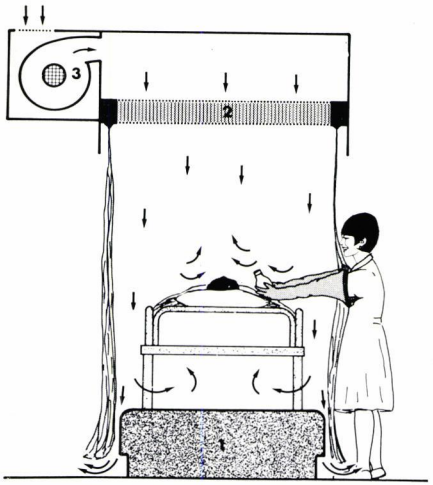
Using a down flow system (inspired on the Vertical Laminar Airflow Curtain Room design; Scandia Laboratories; S.C.-M-69-129 May 1969) and raising of the floor of such an isolation unit (a peracetic acid sterilizable platform was placed inside) it became possible to prevent contamination of the "floor" of the isolator from outside (fig. 3 - 5). At the sides, the unit could to be closed with plastic curtains (fig. 4a and b) (to make reduction of the required air volume and noise possible). Only when free access to the patient was required, one of the sides (curtains) of the unit could be opened without contaminating the inside of the isolator. Before opening of the unit the airflow had to be increased, to make a (turbulent free) stream of air in the opening with a velocity of 50 cm/sec. Handling of the individual inside however, without a "break of the barrier", can only be performed with long sterile rubber or neoprene gloves (fig. 5a and b). Smoke tests have indicated that in such a case, with **one of the side walls open,** the vertical air flow bends inside the unit and leaves it in a horizontal direction through the opening (fig. 5). Introduction of sterile materials into the unit,

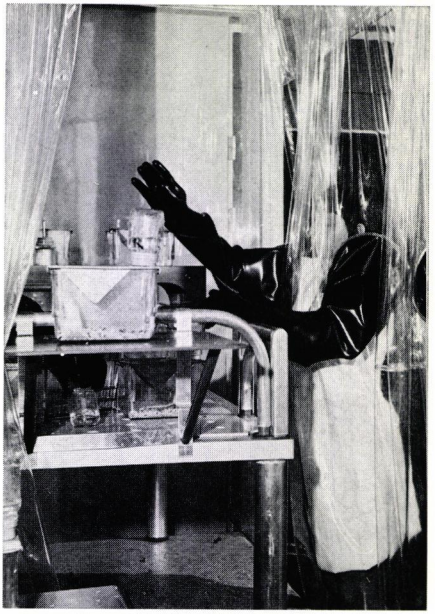


1) platform
2) HEPA-filter
3) soda lime filter
4) peracetic acid fume

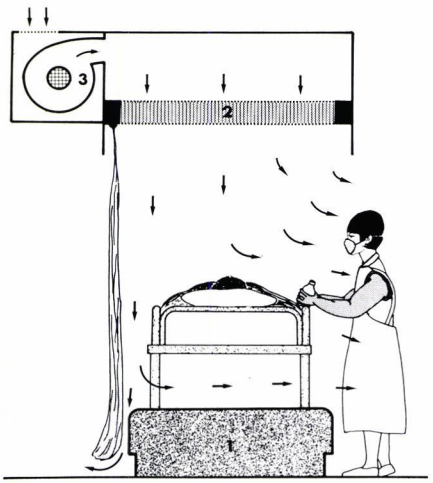
Fig. 3 Diagram of the situation existing during sterilization of the unit.

Fig. 4 Diagram and photo of the unit during handling of an individual inside, using the gloves built into the plastic side walls.





1) platform
2) HEPA-filter
3) blower unit



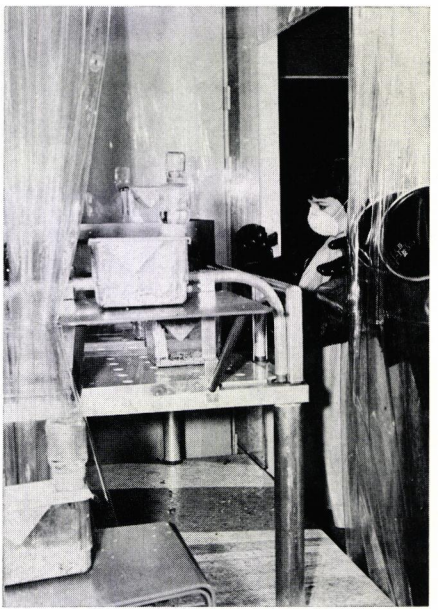


Fig. 5 Diagram and photo of the unit during handling of an individual inside after one of the side walls of the unit has been opened.

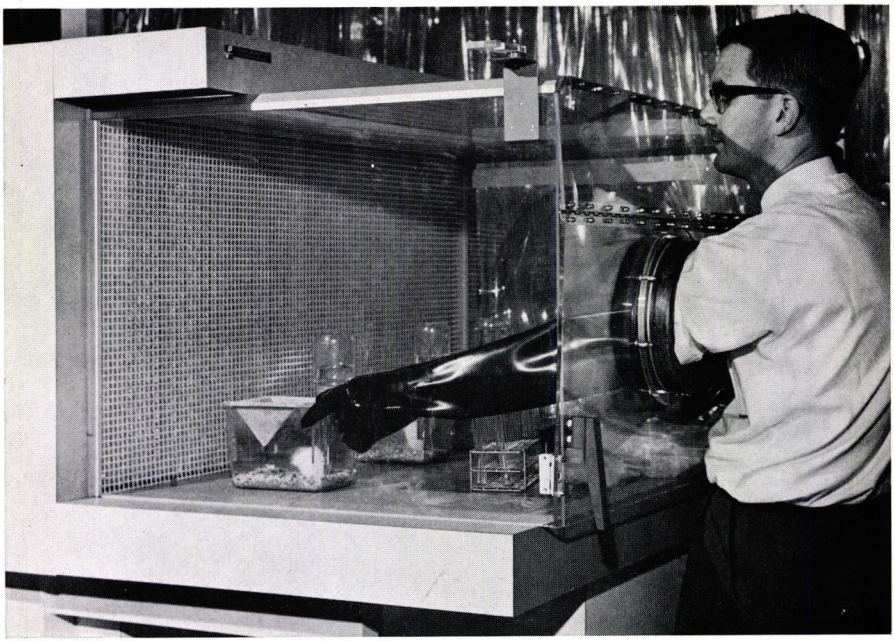


Fig. 6 Manipulations inside the entry lock for materials (cross flow bench) with the "flap" closed.

is performed through a "laminar cross flow bench" which is directly connected to one of the two chambers of the unit (fig. 6 and 7). Also to make reduction of the noise made by the "cross flow bench" possible, it was equiped with a double hinged flap to close most of the open front side if required. The blower speed could then be reduced accordingly.

Fig. 7 Manipulations inside the entry lock for materials (cross flow bench) with the "flap" opened.

A prototype of the unit has been tested for 3 months with germfree mice (see figs. 6 and 7). Thereafter it was used clinically for seven months. The "isolator" is now being manufactured by the firm Pielkenrood Vinitex, Assendelft, The Netherlands, under TNO-supervision.

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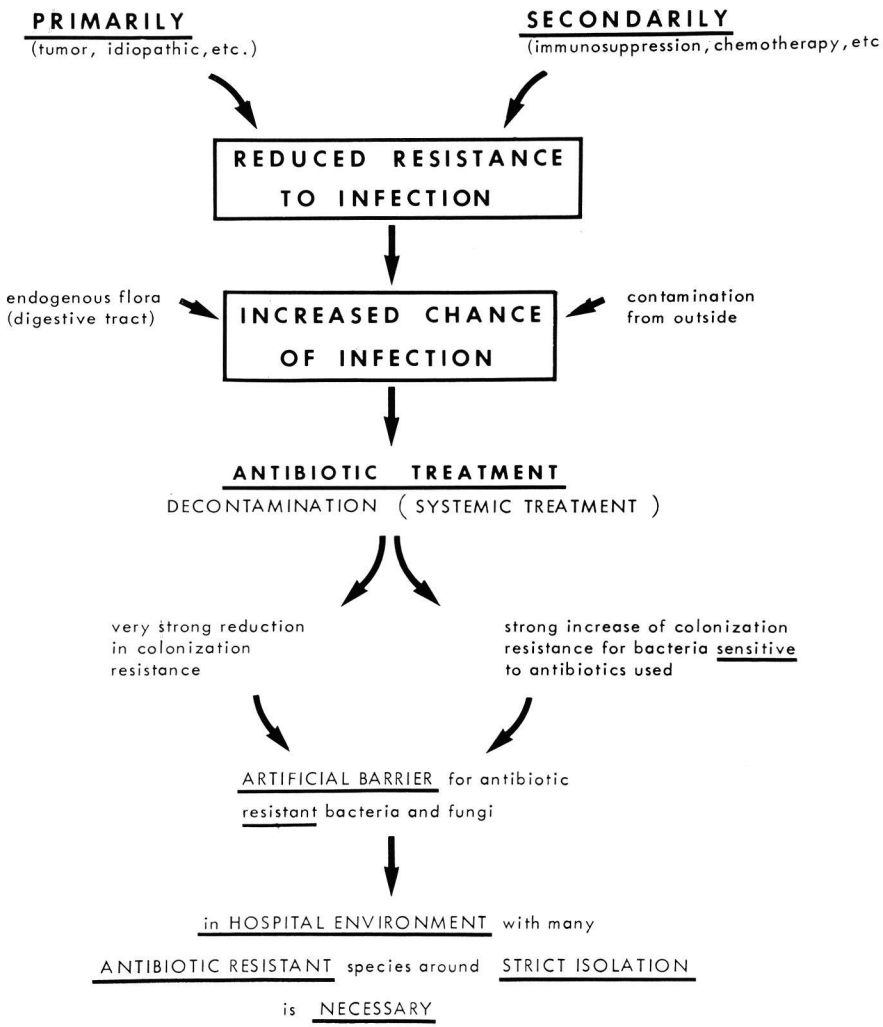
PRIMARILY
(tumor, idiopathic, etc.)
SECONDARILY
(immunosuppression, chemotherapy, etc.)
REDUCED RESISTANCE TO INFECTION
endogenous flora (digestive tract)
INCREASED CHANCE OF INFECTION
contamination from outside
ANTIBIOTIC TREATMENT
DECONTAMINATION (SYSTEMIC TREATMENT)
very strong reduction in colonization resistance
strong increase of colonization resistance for bacteria sensitive to antibiotics used
ARTIFICIAL BARRIER for antibiotic resistant bacteria and fungi
in HOSPITAL ENVIRONMENT with many ANTIBIOTIC RESISTANT species around STRICT ISOLATION is NECESSARY

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