obtained without using such treatment.[6] Moreover, it has not always been possible to show any effect of treatment from kinetic studies of platelet and fibrinogin turnover.[7] Recently the importance of fibrin deposition in the kidney in the pathogenesis of the disease has been questioned.[8 9] The undoubted risk of fatal haemorrhage in association with anticoagulation or thrombolytic treatment makes the need for adequate controlled trials imperative, but the complexity of the trial design and the problem of unnecessary treatment of mildly affected patients have so far proved insurmountable.[3] A further consideration pointing to the need for proper trials is the apparent low incidence of residual hypertension in patients treated with streptokinase.[3] Local infusion, as used in our cases and in those of others,[1] has an advantage of providing the drug in high concentration in the kidney without affecting haemostasis in the rest of the body, and, moreover, if only one kidney is perfused the other can serve as a control. A similar approach to evaluating treatment in cortical necrosis in conditions other than the haemolytic uraemic syndrome is suggested by the second case. The use of the gamma-camera for frequent assessment of renal perfusion and function in impending cortical necrosis would enable only the more seriously affected cases to be treated in this way, whereas those with presumed tubular necrosis alone might be treated conservatively. We cannot yet conclude that the fall in renal perfusion as estimated by dynamic renal scintillography will necessarily lead to cortical necrosis but it is possible to identify these patients with tubular necrosis who have normal or only slightly diminished renal blood flow.

Close collaboration between various disciplines within the hospital service is needed, for without this essential teamwork the treatment of acute renal failure is unlikely to improve.

ADDENDUM—Since this report was prepared we have treated two further children, one aged 14 months and the other 5 months. Both were referred in established renal failure from haemolytic uraemic syndrome and in both cases renal perfusion as judged by the appearance on renal scintillography was extremely poor. It was not known at what time renal perfusion had begun to deteriorate. One child remained alive and well but with chronic renal insufficiency, and there was no difference in individual renal function. The other child died of chronic renal failure after some recovery in renal function, but at necropsy the perfused kidney was smaller than the non-perfused kidney.

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Plastic isolators for treatment of acute leukaemia patients under "germ-free" conditions

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Summary

A gnotobiotic isolation system based on those developed in veterinary research has been constructed for hospital use. Fifteen patients with leukaemia and neutropenia spent a total of 110 weeks in plastic isolators, and none acquired any infection. Endogenous flora was effectively suppressed by topical antiseptics and gastrointestinal decontamination effected with nonabsorbable antibiotics. The isolator system was acceptable to patients and staff and much cheaper than the use of sterile rooms. Other advantages of the system are portability, easy storage, and use on ordinary open wards without prejudice to the microbiological protection afforded. It is as yet uncertain whether protective environments of this type will substantially improve the outcome of treatment for the acute leukaemias.

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Introduction

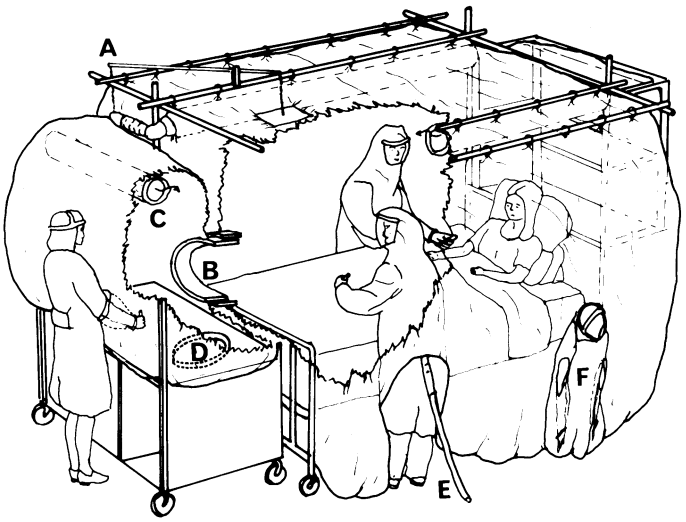
For the past 60 years microbial isolators have been used to maintain a sterile environment in which germ-free animals may be produced for laboratory investigations.[1] These animals are free from bacteria, moulds, and other contaminants in the environment, but some carry vertically transmitted viruses, and the term "gnotobiotic," signifying that their flora is known, is more accurate than the term "germ-free." Colonies of gnotobiotic rats and mice have been maintained continuously since 1954 and a great many species, including calves and foals, have been reared in sterile isolators.[2 3] Experience gained from veterinary gnotobiotic research enabled the development of closed isolator systems using barriers made of flexible plastic film in which many tasks may be performed without violating the microbiological integrity of the system.

Closed-system isolators that are used for the care of patients who are at special risk of infection[4-8] impose restrictions on medical and nursing care because of the interposition of a mechanical barrier between patient and attendants.[9] Hence isolation systems in which a linear flow of sterile air is combined with partial mechanical barriers and reverse barrier nursing techniques have been preferred, even though such systems are microbiologically less secure than closed-system isolators.[9-12] We have designed a patient isolator in which the limitations imposed by the flexible film barrier have been reduced and a linear flow of sterile air has been used solely to protect the port through which sterile supplies are introduced.[13] The security

of this type of isolator has been shown in the rearing of gnotobiotic animals.[2 3 14 15] The isolators can be placed over standard hospital beds in an open ward; no special facilities are necessary for their use and they can be taken down and stored.

Apparatus

The isolator is a rectangular envelope of transparent polyvinylchloride film (0·2-0·3 mm) 1·9 m long, 1·8 m wide, and 2·0 m high supported by a light metal frame attached to the bed. There are two half suits attached to the walls on both sides of the bed. These consist of a clear plastic face piece supported by an adjustable head harness and attached to a conical invagination of the plastic wall which bears the sleeves and gloves. An attendant can enter this half suit and move freely within it, wearing a ventilating vest attached to an air line that provides air for breathing and cooling. The attendant's feet remain on the floor outside the isolator (see fig), but with four suits available any point within the isolator is readily accessible. Supplementary sleeves, terminating in rubber gloves, are attached to the isolator walls and many procedures—for example, adjusting the rate of an intravenous infusion—can be carried out without entering the half suits. The oval entry port (76 × 62 cm) at the foot of the bed is normally held closed by a mating port on a sterile supply isolator (see fig). For entry of the patient the opening between the supply and bed isolators is closed with plastic film, the supply isolator removed, the patient helped in, and the supply unit replaced.



Bed isolator showing patient in bed and two half suits in use. A nurse is working in supply isolator on left. A = Control mechanism for regulating pressure in isolator. B = Patient entry port. C = Air filter for pressurising supply isolator. D = Downflow supply port. E = Air supply to half suit. F = Unoccupied half suit.

ATTACHMENTS

The supply isolator is 1·3 m long, 0·75 m wide, and 1·0 m high and provides space for storing sterile supplies, an electric kettle and a toaster, and for preparation. Supplies are introduced upwards through a horizontal oval port (32 × 28 cm) in the floor of the supply isolator against a stream of sterile air flowing downwards. Smoke tests have confirmed the absence of backflow into the supply isolator. When supplies are introduced a plastic curtain is drawn over the opening into the bed isolator to prevent overinflation, and a supplementary air supply is turned on to provide a sterile air flow of about 100 cubic feet per minute through the supply port. The outer wrap of the double-wrapped sterile supplies is removed in the air stream, the package is introduced, and the inner wrap is removed and discarded through the downflow port. When not in use the downflow port is covered with a plastic bag which also serves a a waste bag.

Small items unsuitable for autoclaving, such as ampoules of drugs and plastic bags containing platelet concentrate, can be rapidly introduced through a flexible tube sealed into the wall at the foot of the bed isolator and immersed in a bath of detergent-hypochlorite. At the foot of the bed on the patient's right a small oval port (32 × 28 cm) is for the removal of soiled materials such as linen and bedpan liners. This port is covered with a sterile polyethylene bag introduced from inside the bed isolator. The bag can be removed and bulky items passed directly to the outside without danger of deflating the isolator since this port will remain open and unobstructed for at least 15 seconds before the pressure within the isolator falls to that of the room outside.

On the left-hand side of the bed the isolator rests on the floor, forming a space 0·6 m wide along the length of the bed, which permits the patient to stand upright and walk and allows room for a chair to be placed underneath the isolator at the foot of the walkway. A bedside table is inserted into a pocket sealed to the wall of the isolator. Pockets in the isolator wall over the head of the bed accommodate shelves that can be reached by the patient and attendants. The mattress is fitted into a pocket in the bottom of the isolator and remains outside the protected space, although the bedclothes can be tucked under the mattress as usual. Since the bed, mattress, and furniture are outside the isolator, sterilisation of the interior of the isolator is readily accomplished with 750 ml of a 2% aqueous solution of peracetic acid, dispersed from an atomizer.[14]

AIR SUPPLY

Filters for sterilising entering and exhaust air are placed at the top of the isolator envelope. Those originally used were 1·8 m long and 7·5 cm in diameter and incorporated three layers of glass-wool filter mat FM004, as in animal isolator units.[14] More recently compact HEPA filters have been used. The blower unit which pressurises the filters is in a sound-absorbing box below the bed and has an alarm system in case of failure (which is extremely rare). The flow of air entering the supply filter is controlled by a ball-valve at the foot of the bed and the flow is indicated on a gauge. The extract filter is connected to the blower through a ball-check valve which is adjusted by a mechanical linkage to the roof of the isolator (see fig) and controls the interior pressure. Slight deflation of the envelope closes the valve and increases pressure within the isolator: conversely, when pressure increases and the isolator roof rises the valve opens and pressure is reduced.

TRANSIT ISOLATOR

An isolated patient may be moved to other parts of the hospital without breaking microbiological isolation by using a transit isolator. This is a tube of thin plastic film, 85 cm in diameter and 3·5 m long, with the ends closed by diaphragms of plastic film the same size as the bed isolator entry port. The transit isolator is placed on a stretcher trolley, the diaphragm and the film closing the entry port are wiped with tincture of iodine and attached together, and an opening is cut for the patient. The patient entry port is closed with fresh film, the end of the transit isolator is tied off, and the two isolators are separated. The patient can re-enter the bed isolator through the diaphragm on the other end of the transit isolator. There are four pairs of sleeves and gloves on the transit isolator, two on each side. Intravenous apparatus is accommodated inside the isolator. Air is sterilised by a small pump and blower attached to the isolator and exhaust air leaves through a flexible tube with an adjustable clamp which controls the interior pressure. As with the bed isolator it is possible to converse with the patient in normal tones while he is in the transit isolator. The transit isolator is sterilised with peracetic acid or by gamma-radiation (2·5 Mrad).

TREATMENT IN ISOLATOR

The impervious plastic film between the patient and his attendants hampers his treatment surprisingly little. Physical examination and the insertion of intravenous lines are carried out through gloves; instruments may be sterilised and passed into the isolator—for example, tongue depressors—or used from outside via invaginations of the plastic—for example, ophthalmoscopes, stethoscopes. An *x*-ray machine can be put in a half suit and the plates placed beneath the plastic film, the entire unit remaining outside the isolator. Sphygmomanometer cuffs and electrocardiograph leads are placed within the isolator: their connections pass out through the plastic wall and the instruments remain outside. The patient can telephone, the receiver being inserted into a sleeve of thin plastic that transmits sound readily, so that sterilisation of the telephone is unnecessary. Sterile bags or bottles of parenteral solutions are aseptically introduced into the

Details of patients with leukaemia treated under gnotobiotic conditions in plastic isolators

Case No.	Age and sex	Diagnosis	Periods of isolation (weeks)	Outcome*
1	25 F	CGL in acute transformation	7	Satisfactory control
			14	Satisfactory control
			3	Died
2	30 F	AML, failed induction therapy	8·5	Complete remission
3	24 M	AMML in late relapse, failed reinduction	3	Died
4	29 F	AML in late relapse, failed reinduction	2	Further failed reinduction
5	54 M	AEL failed induction therapy	3	Died
6	20 F	AMML, failed induction therapy	3	Died
7	57 F	AML, untreated	7	Complete remission
8	49 M	AMML, failed induction therapy	6·5	Died
9	21 F	CGL in chronic phase, intensive chemotherapy	4	Satisfactory control
10	29 F	AMML secondary to chemotherapy for Hodgkin's disease	9	Died
11	20 M	ALL, untreated	3	Complete remission
12	23 M	CGL in chronic phase, intensive chemotherapy	9	Satisfactory control
13	51 F	AML, untreated	9	Died
14	17 M	CGL in acute transformation	12	Died
15	28 M	AML in late relapse, failed reinduction	7·5	Died

CGL = Chronic granulocytic leukaemia. AML = Acute myeloblastic leukaemia. AMML = Acute myelomonocytic leukaemia. AEL = Acute erythroleukaemia. ALL = Acute lymphoblastic leukaemia.
*The term "remission" is applicable only to patients with acute leukaemia.

isolator and attached to hooks in sleeves welded to the roof. The height of these bottles can be adjusted to 1 m above or below the roof level or to any intermediate position.

Preparation of patients

The patient is first decontaminated by reverse barrier nursing combined with sterile food and the use of chlorhexidine preparations —surgical scrub for the skin and hair, mouthwash, and atomized solutions for the ears, nose, and throat. Chlorhexidine douches and obstetric cream are applied to the vulva and oral framycetin, colistin, and nystatin are given to decontaminate gut contents. These measures are continued after entering the isolator and their efficacy is monitored by examining bacteriological specimens from many anatomical sites; swabs of the isolator itself and slit samples of the air inside are also examined for contamination. Chloramphenicol and saline enemas are given 24 and 4 hours before entry to the isolator. Before entry two gloved and gowned nurses place the patient on a sterile sheet on a trolley and spray his entire body, excluding the face, with chlorhexidine aerosol. Another sterile sheet is folded over the patient, who is wheeled to the isolator and helped through the entry port, leaving the sheets behind. Sterile night attire is in the isolator. Once inside, although the patient is in complete physical isolation from the contaminated environment, he may be freely visited by attendants and relatives without need of barrier nursing precautions. There is less psychological isolation within the isolator than under strict reverse barrier nursing conditions, while microbiological isolation is complete. Almost any object can be sterilised by heat, gamma-radiation, or chemicals, and items ranging from soft toys to slide rules have been supplied for the use of patients.

Study

In the past four years we have treated 15 patients in plastic isolators for a total of 110 weeks (see table): all had leukaemia, neutropenia, and an enhanced risk of infection.

Patient acceptance of isolator—We could not predict whether certain patients might be psychologically unsuitable for isolation, so we decided to isolate a patient on the basis of his susceptibility to infection, the status of his leukaemia, and the availability of an isolator. Patients who already had serious infections were not isolated. No patient refused to undergo isolation but most had misgivings. Nevertheless, all 15 patients tolerated isolation well. Most found it much pleasanter than the period of strict reverse barrier nursing that preceded it, and said that they felt less, rather than more, cut off from human contact. Most expressed their willingness to undergo another term of isolation if necessary and one patient was isolated three times over 13 months. Patients who became seriously ill during isolation also became depressed, but their distress appeared no different to that of similarly ill patients nursed under conventional conditions.

Reaction of relatives—The patients' relatives thought that the isolator represented further protection that might improve the chances for successful treatment. Some relatives of dying patients requested that they be removed from isolation, whereas others wanted isolation to be continued to show the patient that hope had not been abandoned. Our policy was to accede to the wishes of relatives.

Acceptance by nursing staff—The isolation equipment was initially viewed with misgivings by our excellent nurses. Most became proficient in the operation of the isolator in a week, and many became most enthusiastic about its use. The nurses agreed that generally the care of an isolator patient was less onerous than the care of a similar patient under conditions of strict reverse barrier nursing. The avoidance of repeated masking, scrubbing, and gowning more than compensated for the inconvenience of working in a half suit. Since nurses carry the main burden of caring for a patient in an isolator their favourable assessment is important.

Attitude of medical staff—Though procedures such as venepuncture were marginally more difficult in an isolator, the ease with which the patient could be seen several times a day more than compensated for this defect.

Bacteriological findings—During isolation repeated bacteriological examinations were made of the urine, stool, and saliva and of swabs from the ears, nose, throat, axilla, umbilicus, groin, and vagina. Faeces were cultured quantitatively by aerobic and anaeorbic techniques and the presence of bacteria was also sought by gas-chromatographic analysis for fatty acids.[16] During 110 weeks of isolation in 15 patients there was no evidence of acquisition of any exogenous micro-organisms, and the patients' endogenous flora remained satisfactorily suppressed and free from potential pathogens such as *Pseudomonas aeruginosa*, the enterobacteriaceae, and *Staphylococcus aureus*. In some patients no residual flora was detectable bacteriologically and in their faeces this finding was confirmed by the gas-chromatographic analyses. Episodes of fever with negative blood cultures were observed and often resolved without explanation of their origin. One case of *Ps aeruginosa* septicaemia was documented; the apparent source of the organism was an old osteomyelitic lesion present before isolation.[17]

Results of leukaemia treatment—Initially we selected patients who had a poor prognosis or were likely to require particularly intensive antileukaemic chemotherapy for treatment in the isolator—for example, those with chronic granulocytic leukaemia in acute transformation or acute myeloid leukaemia in a late relapse. Later some new cases of acute leukaemia and two patients with chronic granulocytic leukaemia in its chronic phase who were undergoing intensive chemotherapy were put in the isolator.[18] These patients were maintained in satisfactory condition, despite extreme neutropenia and immunodepression, for many weeks, and cytotoxic treatment was continued without the intervention of fatal sepsis. Obviously the favourable outcome in some patients could not have occurred had they succombed to infection. On the other hand, in some patients remission of the leukaemia was not secured, even though freedom from infection enabled repeated and aggressive cytotoxic therapy. Thus effective protection from infection is but one facet in the control of leukaemia.

Discussion

The simultaneous application of decontamination of the gastrointestinal tract with antibiotics to reduce endogenous

flora[19] and isolation to prevent the acquisition of exogenous organisms[20] should substantially reduce the risk of infection in neutropenic patients with leukaemia who are receiving cytotoxic drugs. Uncontrolled[21] and controlled[22] studies of protected environments and prophylactic antibiotics in patients with acute leukaemia have shown fewer infective episodes and fewer deaths from infection. Although it was considered that patients so protected could tolerate unusually intensive chemotherapy[21] an increased remission rate was not observed, despite the reduction in deaths from infection.[22] In the controlled study the antileukaemic chemotherapy administered to the isolated patients was identical to that received by the control patients—that is, no advantage was taken of their protected situation by using exceptionally aggressive therapy. Had this been done a higher remission rate might have been observed, although our own experience suggests that this is by no means certain.

In our small and deliberately heterogeneous group of patients, most of whom were selected because of their poor prognosis, the results of the antileukaemic treatment cannot be evaluated. The decontamination and isolation procedures, however, were highly effective, suppressing endogenous pathogens and completely preventing the acquisition of contaminants from the environment. Although we have not shown that such protection can substantially improve the outcome of antileukaemic chemotherapy it is extremely unlikely to make it worse. Extensive studies of intensive chemotherapy in protected environments are required to establish whether improved remission rates can be achieved.

The isolator system proved acceptable to patients, nurses, and medical staff. It is much cheaper than systems that depend on the construction of special rooms, and it can be rapidly dismantled and stored and is easily portable. Plastic isolators may be used in open wards without prejudicing their bacteriological security. Their use on open wards is desirable, since most patients become depressed when nursed for prolonged periods in single rooms, with or without a plastic isolator. Provision of sterile nursing suites based on the use of special rooms is not feasible below a certain size—four such rooms is probably the minimum—but it is easy to operate a single plastic isolator, securing better microbiological protection at much smaller financial outlay. And plastic isolators can be made available in small hospitals as well as in major centres.

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Value of Doppler ultrasound in diagnosis of clinically suspected deep vein thrombosis

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Summary

Doppler ultrasound was used to study 120 legs of 106 patients with suspected deep vein thrombosis (DVT) or pulmonary embolism. Venography was subsequently performed in all. DVT was confirmed by venography in 44 legs and was confined to the calf in 10 of these. Ultrasound detected three calf thromboses and 29 out of 34 more extensive thromboses. Of five undetected thrombi that were proximal to the calf one was associated with partial occlusion and four with extensive collateral circulation. Of the 76 limbs without venographic evidence of thrombosis 21 were thought to have DVT by ultrasound; 18 of these false-positive results could be attributed to external compression of veins, two to excessive tenderness precluding adequate examination; and in one no explanation was found. This test gives more accurate results than judging by clinical signs alone, but users must be aware of its limitations and, particularly, the causes of false-positive and false-negative results.

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Introduction

The clinical diagnosis of deep vein thrombosis (DVT) is inaccurate. Half the thrombi in the calf do not produce signs,[1-4] and 40% of patients with signs have normal veins on venography.[5 6] Most clinical pulmonary emboli arise from veins proximal to the knee,[7-9] and only small silent emboli arise from the calf.[10] Early detection of thrombi in deep veins, particularly those extending into the popliteal and more proximal veins, is therefore essential for the prevention of pulmonary embolism. Some workers have claimed that Doppler ultrasound techniques may detect thrombi early,[11 12] both in routine screening[13 14] and in patients with clinical signs suggestive of venous thrombosis,[15] but others have questioned its value.[16]