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Self-disinfecting plastics for intravenous catheters and prosthetic inserts

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SUMMARY

A disinfectant (2,4,4′-trichloro-2′-hydroxydiphenyl ether: Irgasan, Ciba-Geigy) was incorporated into plastic washers fabricated from ethylvinyl acetate (EVA), polyethylene, polypropylene or TPX. Plastics containing 0·2 and 2% Irgasan gave zones of inhibition on nutrient and blood agar plates seeded with micro-organisms (*Staphylococcus aureus*, *Staph. epidermidis*, *Escherichia coli*, *Proteus mirabilis* or *Candida albicans*) even after thorough washing. Exceptionally, *C. albicans* was inhibited only by 2% Irgasan, and EVA gave good inhibition only against the staphylococci. Similar washers of each plastic were implanted subcutaneously into the flanks of rabbits; before insertion each was washed, had thread woven into it and was surrounded by a plasma clot containing 2×10^8 *Staph. aureus*. All the plastics without Irgasan gave rise to abscesses, none of the plastics impregnated with 2% Irgasan did, though from 2 out of 12 sites small numbers of *Staph. aureus* were isolated at *post mortem*. Using either clinical or bacteriological criteria, the results were highly significant ($P < 0{\cdot}00001$ and $P < 0{\cdot}001$ respectively), demonstrating the effectiveness of this technique in preventing plastic-associated infection.

INTRODUCTION

Infection of plastic artefacts inserted into the body for considerable periods of time – intravenous catheters (Nystrom *et al.* 1983), CSF shunts (Price, 1984), artificial joints (Whyte *et al.* 1981) for example – gives rise to many serious clinical problems and sometimes death. (For further references see e.g., Barrett, 1983.) While proper precautions may reduce the infection rate it seems likely that the impossibility of completely sterilizing the skin and the occurrence of transient bacteraemias will inevitably result in the colonization of the plastic surfaces. In the past, a number of attempts were made to make substances self-sterilizing by the incorporation of disinfectants into their bulk (Miller *et al.* 1962; White, 1962; Towers & Stinson, 1966; Davis, 1969; Taylor, 1970), but these seem to have been discontinued, perhaps because of the limited usefulness of such substances in the

different situation of the dry hospital environment (Kingston & Noble, 1964). We here report laboratory studies which suggest that this might indeed be a useful approach, as suggested previously (Seal & Amos, 1983).

MATERIALS AND METHODS

Materials. The disinfectant used was Irgasan (Ciba-Geigy, registered trade-mark) (2,4,4′-trichloro-2′-hydroxydiphenyl ether), kindly supplied as a free sample by Ciba-Geigy Plastics & Additives Company, Manchester. This was incorporated into the following plastics: polypropylene (Propathene, ICI), polyethylene (Alkathene ICI), TPX (Mitsui & Co. Ltd., London), ethylvinyl acetate (EVA, ICI). The disinfectant powder and the plastic granules were weighed to give the concentrations required, thoroughly mixed, and fed into the moulding machine. The plastic granules melt in the cylinder and the fused material is extruded under pressure into the mould. Irgasan is unaffected by holding at 180 °C for 30 min but in the moulding machine we used (plastic injection moulding machine, Esgo Engineering Ltd), temperatures in the range of 200–300 °C were required. The first work was carried out with polypropylene, with or without Irgasan, moulded commercially into clips 1 × 8 mm (mean) × 20 mm. These (referred to as ' clips ') were small flat pieces of plastic with a central slit, used to clip off fine tubing. However, the shape was slightly inconvenient in the animal model and for later experiments we fabricated polypropylene, and subsequently the other plastics, into washers 10 mm diameter (3 mm diameter hole) and 1 mm thick (' washers ').

Micro-organisms. All of these were isolated from infections, the first three from intravenous plastic catheters: *Staphylococcus aureus* (phage type 83A), *Staph. epidermidis*, *Proteus mirabilis*, *Escherichia coli* (API 20E 5144532) from a urinary tract infection, *Candida albicans* (germ tube positive). For animal experiments, a known abscess-producing strain of *Staph. aureus* (phage type 29, 52) isolated from pigs, was used. Slopes for day-to-day use were replaced from stocks held in liquid nitrogen.

Media. These were Oxoid nutrient broth no. 2 (nutrient broth), Oxoid Columbia agar base (nutrient agar) and this with 5 % defibrinated horse blood added (blood agar).

Zones of inhibition. The ability of the plastics to give zones of inhibition was measured using nutrient agar or blood agar plates flooded with overnight broth cultures of the organisms diluted 10^{-3} in sterile phosphate buffered saline (PBS) (10^{-1} for *C. albicans*). The pieces of plastic (clips or washers) were placed on the plates and stored in a refrigerator for 18–24 h. They were then incubated at 37 °C overnight and the zone of inhibition measured as the width of the zone from the edge of the plastic to the area of full bacterial growth. The effect of washing on the zone size was tested by stirring the pieces of plastic vigorously in PBS containing 1 % Tween 80 and rinsing thoroughly with PBS. Plastics with different concentrations of disinfectant were washed separately. After the first $\frac{1}{4}$ h wash the unused pieces were placed in fresh PBS with 1 % Tween 80 and washed for a further $23\frac{3}{4}$ h and rinsed (' 24 hr wash '). The ability to give inhibition despite prolonged diffusion of the disinfectant was tested as follows. Clips which had been washed for $\frac{1}{4}$ hr were removed and placed on a fresh set of seeded plates, which were stored in a

refrigerator, incubated and read in the standard way. The clips were serially transferred in this way, on average once a week, being stored on the plates in a refrigerator between transfers.

Animal model. The washers had four 1·6 mm holes drilled in them through which black suture silk was woven once and the ends tied together. This was done so as to help retain the clot when in the animal and also because of the potentiating effect of thread in the production of staphylococcal abscesses (Elek & Conen, 1957). Before threading, the washers were washed thoroughly for about 10 min in PBS with 1 % Tween 80 and rinsed in PBS. Plasma clots were made round them using pooled human plasma, hepatitis B antigen negative to reduce the risk of infection to the experimenter, with the following quantities per washer: 1 drop concentrated suspension of *Staph. aureus*, 2×10^8 c.f.u. per drop; 2 drops plasma; 10 μl 1/50 thrombin solution. The washers were immediately implanted subcutaneously in the flanks of young adult New Zealand White rabbits, three per side. Using strict aseptic procedures, a cut was made through the dermis. A pouch was made by inserting a pair of scissors under the dermis and opening them, thus breaking the loose connective tissue between the dermis and the musculature of the thoracic or abdominal cavities. The rabbit dermis has its own associated layer of muscle so that the washer was inserted into the loose connective tissue between these two layers of muscle. The incision was then sutured. With 3 positions (front, middle, back), 2 sides (left, right), 4 different plastics and 3 doses (0, 0·2, 2 %) of disinfectant, it did not prove possible to design an experiment with complete balance, but an almost balanced design was used, with random allocation within the design. The slight lack of balance is allowed for in the analysis. The rabbits were inspected by the medically qualified author (who did not know the code), 10 times in the 18 days during which the experiment ran and any abscesses swabbed. On the seventh day any site showing swelling was sampled by injecting sterile PBS and aspirating. On the 18th day the animals were killed and the sites of implantation opened and swabbed. The washers were removed, unless they had been lost from a discharging abscess, and tested for their ability to give zones of inhibition on nutrient agar plates seeded with *Staph. aureus*. Bacteriological samples were plated on blood agar, *Staph. aureus* being identified by colonial appearance; at least one isolate from each lesion was tested for coagulase production.

Foreign body reaction. To test for this, six uninfected polypropylene washers were implanted subcutaneously into a rabbit, as had been done for infected washers. The pairs of washers for each level of disinfectant (0, 0·2, 2 %) were washed separately in sterile PBS with 1 % Tween 80 using a rotary mixer, and rinsed thoroughly with sterile PBS. After 19 days in the rabbit, the animal was killed and squares of skin each containing a washer cut out and fixed in neutral formol saline. The tissue was processed still containing the plastic washer. Sections were cut from levels of the blocks containing the washer and stained with haematoxylin and eosin. They were examined by a consultant histopathologist who did not know the Irgasan content of the washers, together with sections of two areas of normal skin from the flank of the same rabbit.

Table 1. *Zones of inhibition given by polypropylene clips containing Irgasan – effect of organism, medium and length of washing*

	Width of zone from edge of plastic in mm					
	Blood agar			Nutrient agar		
% of Irgasan	0	2	4	0	2	4
Staph. aureus						
0 wash	1	13	13	nd	∞	∞
¼ h wash	0	11	12	nd	∞	∞
24 h wash	0	nd	12	nd	∞	∞
Staph. epidermidis						
0 wash	1	14	16	3	25	25
¼ h wash	0	14	15	2	22	25
24 h wash	0	nd	14	tr	20	20
Esch. coli						
0 wash	0	5	7	tr	16	15
¼ h wash	0	5	5	0	12	12
24 h wash	0	nd	4	0	10	10
Proteus mirabilis						
0 wash	0	5	5	0	13	13
¼ h wash	0	3	4	0	11	11
24 h wash	0	nd	4	0	9	10
Candida albicans						
0 wash	0	1	2	0	5	7
¼ h wash	0	1	1	0	4	5
24 h wash	0	nd	0·7	0	4	3

nd, not done (or not measurable); ∞, too big to measure; tr, trace.

RESULTS

Experiments to determine the inhibitory effect of Irgasan incorporated into plastic, and its persistence despite continued effusion from the plastic, were carried out mainly with polypropylene. The first experiments were carried out with clips. Table 1 shows that a wide range of organisms are inhibited, that the presence of blood in the medium reduces but does not abolish the inhibition, and that the effect is not abolished by vigorous washing for 24 h. Serial transfer of the clips which had been washed for ¼ h was carried out as described. In all, 11 transfers were made, the last 83 days after the initial washing experiment. The zones of inhibition were plotted against time (Fig. 1). The only decrease found was with *C. albicans* (small zone on blood agar lost by about 30 days, that on nutrient agar falling over the 83 days from about 4 and 5 mm for 2 and 4 % Irgasan to about 1 and 3 mm).

The effect of pre-diffusion was examined in two ways. For the first, the plates (nutrient agar), were prepared in the standard way (clips and diluted *Staph. aureus* culture added together) but then stored at 4 °C for varying lengths of time. For the second, the clips were placed on the nutrient agar and stored at 4 °C for various lengths of time before the plates were flooded with the diluted *Staph. aureus* culture and incubated directly. The entire zone of clearing was traced onto graph paper. Neither method showed any effect of pre-diffusion: for the first method the areas

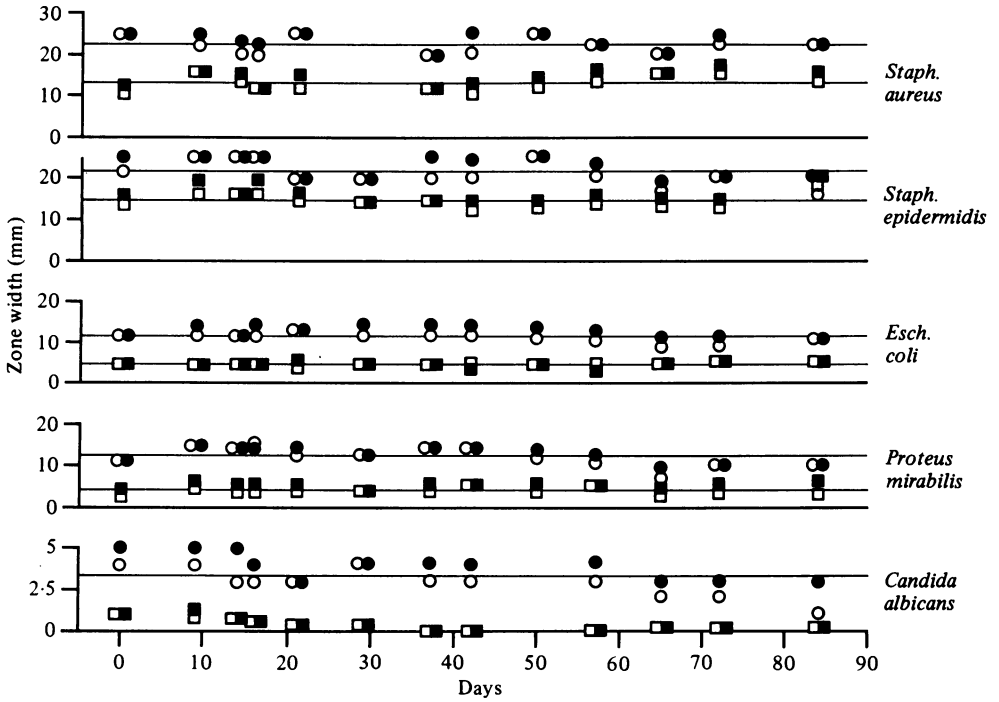


Fig. 1. Zone width (in mm) from edge of clip during serial transfer on nutrient or blood agar inoculated with *Staph. aureus*, *Staph. epidermidis*, *Esch. coli*, *Proteus mirabilis* or *Candida albicans*. ●, Clip containing 4% Irgasan on nutrient agar; ○, clip containing 2% Irgasan on nutrient agar; ■, clip containing 4% Irgasan on blood agar; □, clip containing 2% Irgasan on blood agar. Where the zone was too big to be measurable, it has been (arbitrarily) plotted at 25 mm.

(in square inches) for 0, 1, 4, 8 and 24 h pre-diffusion were 3·9, 4·1, 4·1, 4·3, 3·8 (mean 4·0, σ_{n-1} 0·20). In the second method the results for the same times were 4·0, 3·7, 3·9, 3·9, 3·4 (mean 3·8, σ_{n-1} 0·24). The overall mean and standard deviation was 3·9 and 0·24.

Because the preliminary experiments with the animal model showed that the clips were inconvenient to manipulate, all further experiments were carried out using plastics fabricated into washers.

The experiments described above (see Fig. 1) showed a negligible difference in zone size with a reduction in the concentration of Irgasan in the plastic clips from 4 to 2%. Experiments were therefore carried out on nutrient agar only, using polypropylene washers containing 0·02, 0·2 and 2% Irgasan, which were twice carefully washed before testing (Table 2), and were subsequently given one serial transfer. Because preliminary animal experiments suggested that 0·02% Irgasan did not prevent infection and these experiments suggested that at this concentration disinfectant activity was rapidly reduced on transfer, further experiments were confined to washers containing 0·2 and 2% Irgasan. The range of plastics was extended and the results are summarized in Table 3.

Because of the relatively small zones of inhibition given by washers fabricated with EVA, material eluted with 50:50 methanol: 0·01 N HCl from pulverized EVA

Table 2. *Zones of inhibition on nutrient agar given by polypropylene washers containing Irgasan*

	Zone width in mm*			
% Irgasan	0	0·02	0·2	2
Staph. aureus	3 (0)	10 (6)	11 (11)	18 (19)
Staph. epidermidis	tr (0)	8 (5)	9 (9)	14 (16)
Esch. coli	0 (0)	4 (1)	5 (4)	10 (10)
Proteus mirabilis	0 (0)	3 (tr)	4 (4)	9 (10)
Candida albicans	0 (0)	0 (0)	1 (0)	4 (4)

* The zone width (mm) is measured from the edge of the plastic to the start of full bacterial growth.

Figures in parentheses are washers retested on a second plate.

tr, trace.

Table 3. *Zones of inhibition given by Irgasan incorporated into washers of different plastics. Lawns on blood agar (BA) and nutrient agar (NA)*

	Width of zone from edge of plastic in mm															
Plastic	Polypropylene				Ethylvinylacetate				Polyethylene				TPX			
% Irgasan	0·2		2		0·2		2		0·2		2		0·2		2	
	BA	NA	BA	NA	BA	NA	BA	NA	BA	NA	BA	NA	BA	NA	BA	NA
Staph. aureus																
0 *wash*	8	16†	14	21	1	2	4	8	6	17	10	22	5	16	11	26
¼ h wash	7	17	11	20	1	2	3	8	6	16	9	21	5	13	9	21
24 h wash	4	9	7	13	0	1	3	7	4	11	7	16	3	11	6	17
Staph. epidermidis																
0 wash	9	16	14	21	1	1	4	8	7	16	11	22	7	14	14	21
¼ h wash	8	14	11	19	1	2	3	8	7	15	10	20	7	13	12	17
24 h wash	4	9	8	14	tr	1	4	7	5	10	8	16	4	8	9	13
Esch. coli																
0 wash	3	8	5	13	0	0	1	1	3	9	5	14	2	8	5	13
¼ h wash	2	6	3	9	0	0	0	1	3	9	4	12	1	5	3	8
24 h wash	1	4	2	7	0	0	0	tr	1	4	3	9	1	2	2	5
Proteus mirabilis																
0 wash	2	7	5	13	0	0	0	0	2	8	4	13	1	3	4	12
¼ h wash	1	6	2	9	0	0	0	0	2	7	4	12	tr	3	2	7
24 h wash	tr	3	2	6	0	0	0	0	1	3	3	9	tr	1	1	5
Candida albicans																
0 wash	0	1	1	6	0	0	0	0	0	1	1	5	0	0	1	4
¼ h wash	0	tr	tr	2	0	0	0	0	0	tr	1	4	0	0	0	1
24 h wash	0	0	0	tr	0	0	0	0	0	0	tr	1	0	0	0	0

tr, trace.

and polypropylene was examined for its u.v. spectrum. The 280 nm peak given by Irgasan was present in the eluate from the plastics which contained Irgasan and no evidence of breakdown products was found. Exact comparison of Irgasan concentrations was not possible by this method because the relative efficiency of effusion was not known, but these results suggest (rather than prove) that there

Table 4. *Zones of inhibition given by polypropylene washers containing Irgasan after subcutaneous implantation in rabbits*

% Irgasan in washer	Zone width in mm*		
	12 days† in animal	29 days† in animal	293 days‡ in animal
0	0 (0)	0 (0)	0 (0)
0	0 (0)	0 (0)	0 (0)
0·2	4 (5)	0 (4)	0 (tr)
0·2	5 (5)	0 (4)	0 (1)
2	9 (10)	6 (9)	3 (5)
2	11 (10)	6 (10)	4 (5)
Not implanted§			
0	0 (0)		nd
0·2	15 (13)		16 (12) 16 (12)
2	20 (18)		nd

Nutrient agar seeded with *Staph. aureus.*

nd, not done; tr, trace.

* Width of zones from edge of washer given in mm. Values in brackets are those found in a repeated measurement after the washers had been thoroughly cleaned.

† Both these sets of washers were tested at the same time after having been stored in screw capped bottles in a refrigerator for 22 and 5 days respectively.

‡ Small portions of the fibrous capsule were tested for their ability to give zones of inhibition. A small zone was found with tissue from 1 of the 2 implants containing 2% Irgasan.

§ These washers were from the same batch as those implanted in the rabbits, but stored dry in the laboratory during the length of the experiment.

was no substantial decomposition of Irgasan in the EVA washers, which required the highest moulding temperature.

Animal experiments

The serial transfer experiments can be criticized in that diffusion takes place from one surface only and might in other ways differ from diffusion *in vivo*. Accordingly washers which had been implanted subcutaneously in rabbits for various lengths of time were tested (Table 4). Other experiments showed that careful cleaning of the implanted washers often increased the zone of inhibition and that tissue scraped off implanted washers containing 2% Irgasan itself gave zones of inhibition about 10 mm wide measured from the edge of the small heap of tissue.

As these experiments on the ability of Irgasan-containing plastics to inhibit bacterial growth on agar were very encouraging, an animal model to test their effectiveness in preventing infection *in vivo* was developed. The results of the definitive experiment are given in Tables 5 and 6. Table 5 gives the proportions of sites infected with the different classes of washers. The washers which did not contain disinfectant all gave rise to obvious severe infection. Large abscesses occurred round them between days 4 and 14 which usually resulted in the extrusion of the washer. Severe cellulitis occasionally occurred, as did massive suppuration. All the washers containing 2% Irgasan gave completely healed scars with no evidence of infection around them. At *post mortem* small numbers of *Staph. aureus*

Table 5. *Proportion of washers causing infection after subcutaneous implantation into the flanks of rabbits*

Plastic	% Irgasan	Infection (Clinical diagnosis)	*Staph. aureus* isolated
Ethylvinyl chloride	0	2/2	2/2
	0·2	4/4	4/4
	2	0/3	0/3
Polyethylene	0	4/4	4/4
	0·2	0/2	1/2
	2	0/3	1/3
Polypropylene	0	4/4	4/4
	0·2	1/2	1/2
	2	0/3	0/3
TPX	0	2/2	2/2
	0·2	4/4	3/4
	2	0/3	1/3

Each washer was surrounded by a plasma clot containing 2×10^8 c.f.u. of *Staph. aureus*. 2/2 etc – 2 out of 2 implanted washers.

Table 6. *Zones of inhibition given by washers recovered at* post mortem *and their associated tissue. Lawn of* Staph. aureus (*animal strain*) *on nutrient agar*

	Zone size in mm		
% of Irgasan	0	0·2	2
Ethylvinylacetate			
unimplanted washer	nd	2	8
Post mortem washer	0 nf	nd, nf, nf, nf	3, 2, 3
associated tissue	0 (nf)	0, (nf), (nf), (nf)	+ +, +, + +
Polyethylene			
unimplanted washer	nd	16	21
Post mortem washer	nf, nf, 0, nf	0, 0	0, 0, 0
associated tissue	(nf) (nf) nd (nf)	0, 0	0, 0, 0
Polypropylene			
unimplanted washer	nd	17	20
Post mortem washer	nf, nf, 0, nf	3, 3	6, 6, 6
associated tissue	(nf) (nf) 0 (nf)	0, + + +	+ +, + +, 0
TPX			
unimplanted washer	nd	13	21
Post mortem washer	nf, nf,	nf, 4, nf, nf	7, 7, nd
associated tissue	(nf) (nf)	(nf) nd, (nf) (nf)	tr, + + +, nd

nf, washer not found at *post mortem*. In all instances this loss was associated with clinical infection. Of the 21 clinically infected sites, 15 had extruded their washers.

nd, test not done.

Unimplanted washers were tested after thorough washing.

were occasionally found in the implantation sites where no clinical infection had been seen (100 colonies per plate or fewer). On one occasion there was what seemed to be pus, but this was sterile (TPX with 0·2% Irgasan). It was noted (Table 6) as had been shown before (Table 4) that reduced zones of inhibition were given by the washers, and that material adherent to discs containing disinfectant often

gave zones of inhibition. An unexpected finding was that none of the polyethylene discs gave any zones of inhibition at all, suggesting a higher rate of effusion from this plastic.

Analysis was performed using the 'Glim' computer package (Baker & Nelder, 1978), treating the underlying statistical distribution as being binomial. There appeared to be no evidence of difference between animals, between types of plastic, between front, middle and back positions, or between left and right positions. The observations were then combined over these features.

A strong relationship with Irgasan content of the plastic was found whether judged by clinical result ($P < 0{\cdot}00001$) or by bacteriological result ($P < 0{\cdot}001$) the zero dose always leading to an 'infected' result, the 2% dose always (clinically) or nearly always (bacteriologically) to an 'uninfected' result, the 0·2% dose giving 75% infected.

Unfortunately, a further variable, that could not be planned for in the design, could be important. This is the presence or absence of the plastic washer at the time of *post mortem*. This was also strongly related to the dose, being always present for the 2% dose, absent 11 times out of 12 for the zero dose, and present half the time with the 0·2% dose.

The presence or absence of the washer is thus so confounded with the strength of the disinfectant dose that the statistical evidence for which of the two is responsible for the observed results is weak. However, on common-sense grounds, it seems likely that the disinfectant prevents infection and that this, in turn, leads to the retention of the plastic. Any other cause-and-effect relationship between these three features seems extremely far-fetched.

The histopathologist who examined the reaction around uninfected polypropylene reported that for all six specimens the disc space was seen surrounded by a fibrous sheath with a lining of cells, probably histiocytic in nature. Very little inflammation was seen in any of the specimens. The two samples with washers containing 2% Irgasan had slightly more inflammation than the others but in none of them was the degree of inflammation more than mild. These histological appearances are illustrated in Fig. 2. When the six polypropylene washers were removed after 293 days subcutaneously in a rabbit to test for their continuing ability to inhibit *Staph. aureus* (Table 4), they were contained in thin transparent fibrous envelopes. There was no obvious inflammation as seen by the naked eye, but it was not possible to carry out histological examination.

DISCUSSION

The usefulness of tests for evaluating disinfectants depends on these tests mimicking sufficiently closely the conditions under which they will have to work in practice. We think that the tests we have developed, both *in vitro* and *in vivo* adequately represent the clinical situation.

The aim of self-disinfecting materials for intravenous catheters and plastic prostheses is to prevent the growth of any micro-organism which might lodge on or near the surface. Body fluids (or fibrin clots) will provide a medium for growth of the micro-organisms and a continuous liquid pathway for the disinfectant to effuse from the plastic into the micro-organism. Thus measuring the ability of

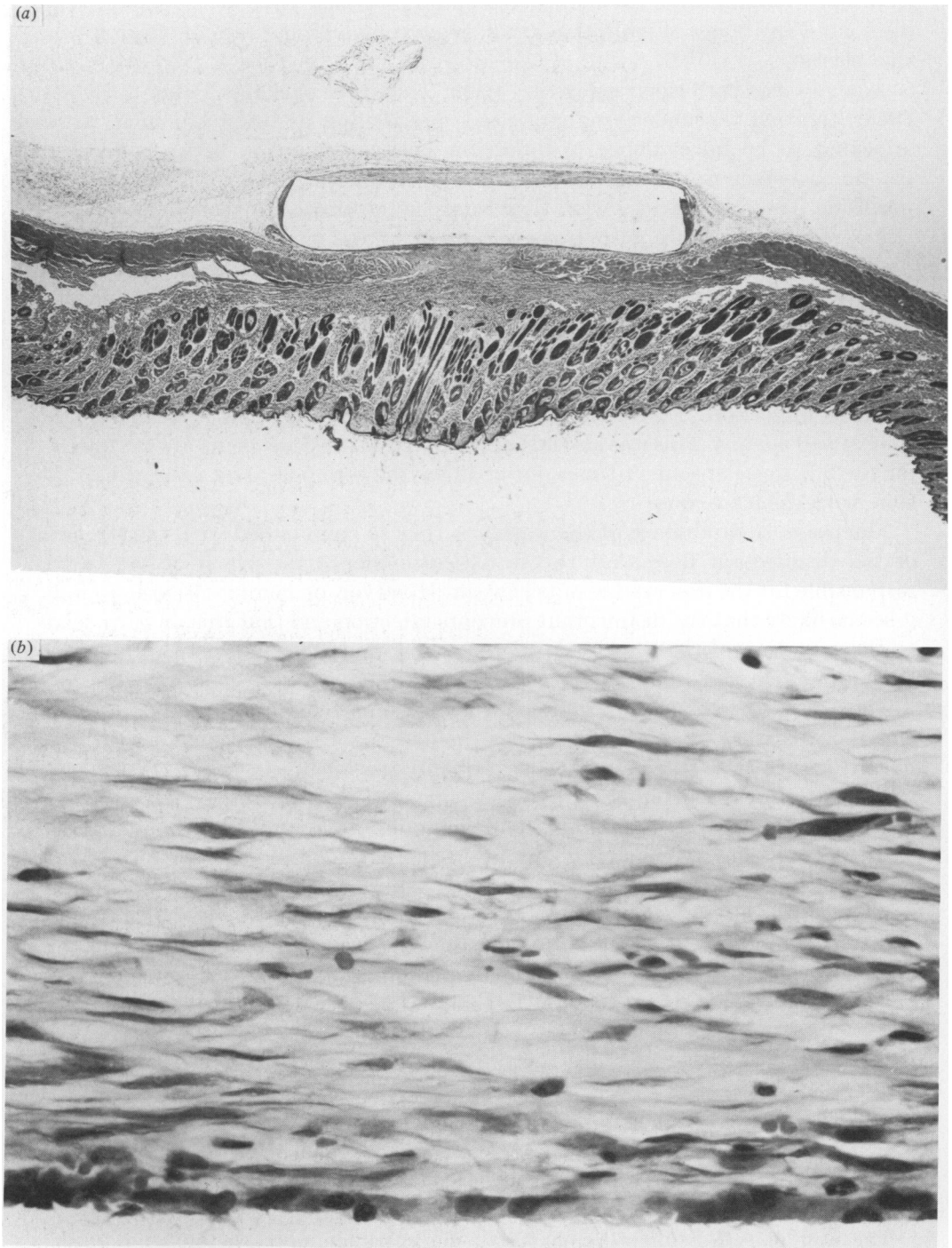
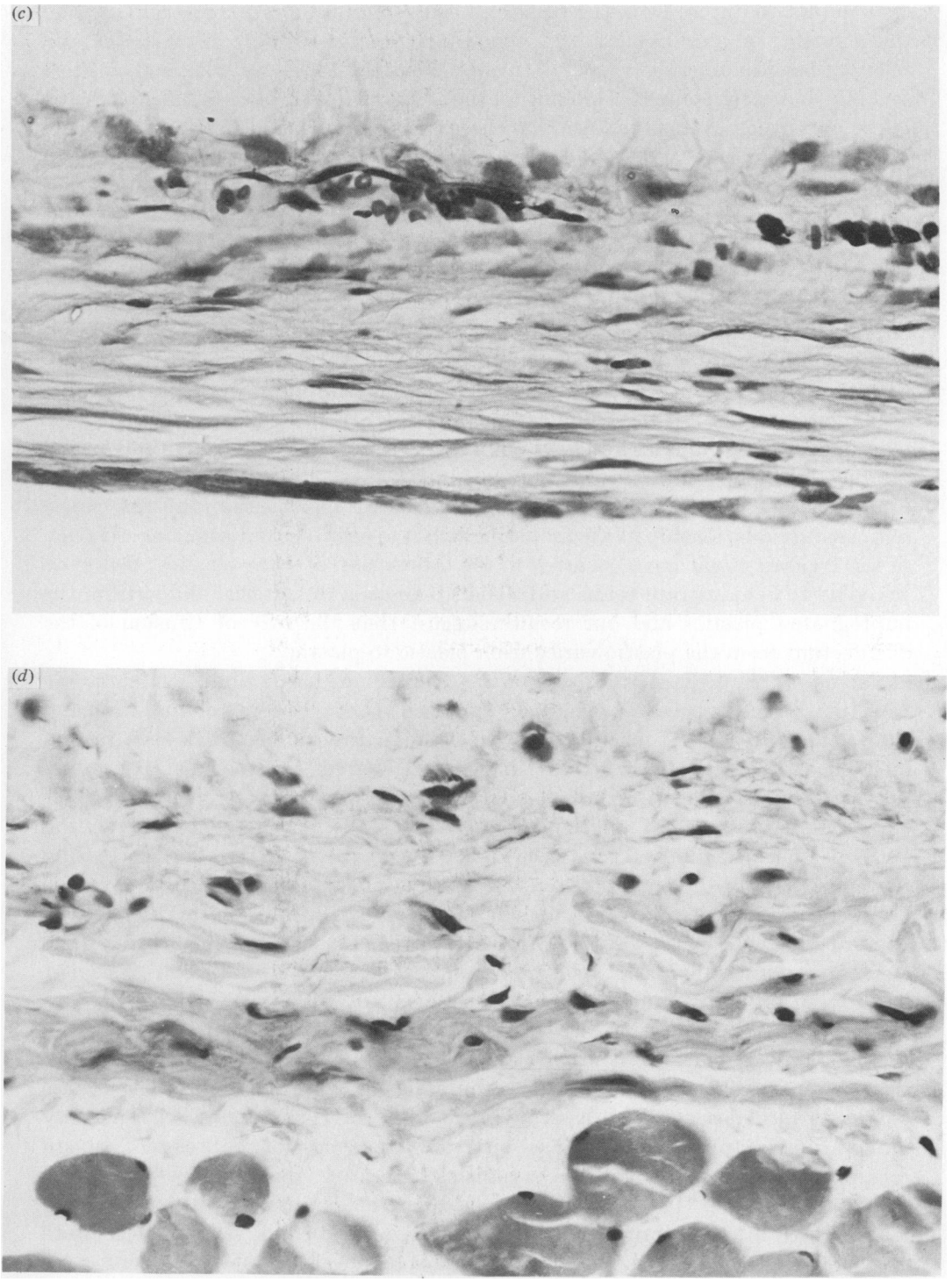


Fig. 2. Sections of rabbit skin containing polypropylene washers (H & E). (*a*) Low power photograph showing pocket containing polypropylene washer with 2% Irgasan. (The polypropylene is present in the block but does not adhere to the slide.) × 10. (*b*) High power photograph of (*a*) showing cells lining pocket and part of fibrous sheath. Same



orientation. × 550. (*c*) High power photograph of pocket containing polypropylene washer without Irgasan, otherwise as for (*b*). × 550. (*d*) High power photograph of normal skin. Orientation as for (*a–c*). × 550.

disinfectant to diffuse from the plastic to cause inhibition of micro-organisms on the nutrient, or more realistically, blood agar, seems to us to be a simple and relevant test. In an earlier paper (Kingston & Noble, 1964), we criticized this test severely, but in the context of looking for the ability of dry surfaces to kill dust-borne micro-organisms. We have shown that three plastics (polyethylene, polypropylene, TPX) containing 0·2 and 2% Irgasan give zones of inhibition with organisms of widely varying properties, all of which can be associated with catheter and other plastic-associated infections. The fourth plastic (EVA) gave substantial (but smaller) zones of inhibition with *Staph. aureus* and *Staph. epidermidis* but not effectively with the other organisms. Incorporation of 5% horse blood into the medium reduced but did not abolish the zones of inhibition. It is obviously important that the disinfectant continues to be inhibitory for a considerable period of time and this we have also shown in several different ways, most thoroughly with the polypropylene. It is striking that zones of inhibition were found against *Staph. aureus* after 293 days in a rabbit (Table 4). We used standard small scale manufacturing techniques and have shown that these produce a potentially useful product. Developmental research on this aspect could usefully be done. The conditions we employed for moulding precluded exact study of the time–temperature relationship in the moulding and it is possible that some inactivation of the Irgasan might have occurred in the fabrication of some plastics. However, we failed to demonstrate peaks additional to Irgasan in material eluted from the impregnated plastics and our results suggest that the rate of effusion of the disinfectant from the plastic varies from plastic to plastic.

The use of the 24 h pre-diffusion of the disinfectant needs some comment. We used this originally because we had not expected such large zones of inhibition and wanted to increase the sensitivity of the system. Pre-diffusion has been recommended (though for shorter periods) in antibiotic testing, and the ideal time would (in our system) depend on when contamination was expected to occur. Our experiments showed that length of pre-diffusion made no difference. The relation between concentration and zone size (Tables 1, 2 and 3) is also puzzling. Increasing the concentration of Irgasan from 0·2 to 2% increased the width on average between 1·4- and 1·7-fold (TPX on blood agar about 2-fold). In this system the bactericidal agent has to diffuse to the surface of the plastic and then through the agar. The simple square root relation found in testing antibiotics where the agent has only to diffuse through the agar clearly does not hold.

The animal experiments are clearly also very promising but need comment. Two approaches were considered. In the first *Staph. aureus* was allowed to adhere to the plastic from a suspension in PBS, representing contamination of the plastic before fibrin deposition had occurred. However, polythene infected in this way did not give rise to abscesses in the rabbit in our hands, possibly because not enough organisms adhered (about 10^6 organisms, counted using a 5-[^{125}I]Iodo-2^1-deoxyuridine label). The technique we used here represents organisms becoming incorporated into the fibrin clot during bacteraemia. Since the staphylococci were protected by the clot, it is likely to be a more severe test of the self-disinfecting activity of the plastic, and also has the advantage that it is easy to vary the size of the inoculum. The results with this model were highly significant. The clot will be to some extent dispersed on the insertion of the plastic washer and it is,

therefore, not suprising that there is some discrepancy between clinical and bacteriological diagnosis of infection. There was discrepancy on four occasions. In three of them small numbers of *Staph. aureus* persisted under the skin but the wound had healed. In the other, pus had formed but was sterile. Despite these slight irregularities we can assert that these self-disinfecting plastic washers can prevent infection occurring with 2×10^8 c.f.u. of abscess-forming *Staph. aureus*. This is far larger than the number of organisms that will be present as the result of surgery, or bacteraemia. It may be that less Irgasan, say 0·2%, would be sufficient to repress infection with the lower numbers of organisms likely to be found in clinical practice.

The tests on the washers removed at *post mortem* (Table 6) showed that tissue surrounding washers containing Irgasan itself gave zones of inhibition in most instances indicating that the inhibitory activity of the plastic can diffuse some way from it *in vivo*. Thus it is possible that organisms attaching to a fibrous capsule surrounding the insert could also be killed. The occasional failures were probably due to the tissue originally surrounding the washer being replaced during extraction of the washer.

We must emphasize that we have only preliminary though encouraging results on the lack of long term irritant and toxic effects of these plastics (Fig. 2). (We note that Chalkley, Sarnat & Shoch, 1966, using polymethylmethacrylate impregnated with 3% hexachlorophene and 1% 'Corobex CP-4' found that 'The germicide-impregnated lenses were no more irritating to the eye than ordinary contact lenses.') Irgasan itself has undergone extensive toxicity testing (Ciba-Geigy, 1974). We also have preliminary evidence that different plastics vary substantially in the length of time during which they remain inhibitory. Though we have obtained good results with Irgasan, there are probably other disinfectants which would work as well. Indeed Towers & Stinson (1966) found promising preliminary results in a goat animal model using metal implants coated with PVA containing dibromopropamidine.

Until recently, intravascular catheters have been produced from 'Teflon' which cannot be impregnated with disinfectant. However, medical quality polyester-based polymer and ether-based polymer are now being tried in the United States of America instead of 'Teflon'. These polymers can be impregnated so that it may soon be possible to test the effectiveness of this technique in preventing infection associated with intravascular plastic catheters, as well as plastic prostheses. We do not claim to have produced the definitive self-disinfecting plastic, but we have shown that self-disinfecting plastics can be produced that will stand up to rigorous bacteriological investigation *in vitro* and *in vivo*. We believe that this paper presents sufficient evidence to justify developmental work including toxicity studies and in-use evaluation.

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