A STUDY OF THE CHEMICAL COMPOSITION AND POTENTIAL HAZARDS OF AN ANTIFOAM SUBSTANCE USED IN INTRACARDIAC SURGERY

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Silicone fluids have been extensively used in certain heart-lung machines in order to remove bubbles produced by the mechanical oxygenation of the blood. The antifoaming technique involves the passing of oxygenated blood over a filmed surface or through a mesh or sponge treated with antifoam material. This is done to prevent air emboli which might occur if bubbles were allowed to enter the circulation.

The method of oxygenation used in the unit in which this work was done is the DeWall type of bubble oxygenator. A cursory examination of a proprietary antifoaming material originally used in this type of oxygenator in Johannesburg showed the presence of considerable amounts of particulate material consisting largely of finely divided amorphous silica (about 200 Å in diameter). Apart from the possibility of these particles aggregating to form still larger particles which could result in capillary occlusion, it is considered that the toxic action of the finely divided silica constitutes a very real hazard. The phenomenon of " silica shock " caused by the intravenous injection of finely divided amorphous silica of particle diameter 200–500 Å into experimental animals has been known since the work of Gye and Kettle in 1922, and has since been widely confirmed by many workers. Work done in this laboratory (Harington and Sutton, 1961 ; Harington, 1961) leaves little doubt that silica of this particle size can, even at low concentrations, produce rapid and serious physiological defects.

In view of the above evidence, a detailed chemical analysis was made of the antifoaming material being used here, and a simple procedure is described by means of which particulate material in antifoam preparations can be removed.

ANALYSIS OF ANTIFOAM PREPARATIONS

Two proprietary antifoam preparations have been used in bubble-oxygenator types of heart-lung apparatus. The first one, antifoam A, has been widely used since the development of artificial heart-lung by-pass surgery. In some of the large number of papers on this branch of surgery, it has been described as a potent, non-toxic, antifoam silicone substance, while in others it has not been mentioned. Clark, Gupta, and Gollan, who introduced the bubble-oxygenator type of heart-lung machine in 1950, advocated the use of " generous amounts " of the substance before by-pass on dogs.

Antifoam A as found in the tin is a viscous, greyish, oil-like material which, when made up to a concentration of 5% (w/v) in ether, yields on centrifugation a particulate sediment of 0.9 g./100 ml. solution.

Antifoam XC-20033 has been used in bubble-oxygenators in a great number of successful operations (Lillehei, Warden, DeWall, Stanley, and Varco, 1957). In the tin it appears as a heavy, greyish-white paste-like material, and, when made up to 5% (w/v) in ether and centrifuged, yields a sediment containing 0.5 g. particulate material/100 ml. solution. It has been used in Johannesburg in the past and forms the basis of the present investigation. The solutions for use and analysis were prepared according to a standard procedure as follows :

Fifty grammes of antifoam from the tin was dissolved in a few hundred millilitres of ether, stirred well, and allowed to stand for about 48 hours. The supernatant fluid was decanted and more ether added, after which the mixture was again allowed to stand. This was repeated three or four times, until about a litre of ether had been used. The supernatant fluid should be clear when decanted, and, if not, should be centrifuged at 2,000 r.p.m. for 10 minutes in a refrigerated centrifuge. The clear supernatant was then used as antifoaming material.

Antifoam solutions for chemical analysis were prepared exactly according to the above directions. Unfortunately, as will be shown, centrifugation at the speed suggested in the above procedure will not produce a clear supernatant and far higher speeds are required.

ANALYSIS FOR SILICA OF ANTIFOAM XC-20033

Preparations of 5% and 10% antifoam in ether (w/v) were made by the above method. The final

solution gave the appearance of slightly viscous, turbid solution (about the turbidity of a 1:2 water-milk mixture). Centrifugation at 2,000 r.p.m. did not clear the solution in any way. This solution/suspension consists of pure silicone antifoam in true solution in the ether solvent, together with a suspension of ether-insoluble particulate material responsible for the pronounced turbidity, and will be referred to as " turbid antifoam.". High-speed refrigerated centrifugation of an aliquot (10,000 r.p.m. for 15 min.) yielded a clear centrifugate and a white amorphous sediment at the bottom of the tube. The clear centrifugate contained pure silicone in true solution, and is referred to here as " clear antifoam." The sediment was washed six times in ether to remove any traces of silicone on the surface of the particles, dried *in vacuo,* and examined. This is referred to as " sediment."

RESULTS OF ANALYSIS

SILICA CONTENT.—Silica was determined by the standard ammonium molybdate method after fusion with sodium carbonate. It was found necessary to exercise great care in maintaining constant volumes of the ethereal solutions during preparation and analysis, and at the start of the work false high results were obtained, due to ether evaporating on standing and on centrifugation at room temperature. These difficulties were overcome by carefully and immediately closing all flasks after use, and by using a refrigerated centrifuge.

Random samples of antifoam XC-20033 from two 1 lb. tins (referred to as tin A and tin B in Table I) were taken and weighed directly into platinum crucibles (No. 1 in Table I). The sediment obtained after high-speed centrifugation was treated in a similar way (No. 4 in Table I).

In the case of the ethereal solutions (turbid and clear antifoam), known volumes of well-shaken standard solutions of known concentration were accurately and rapidly pipetted into platinum crucibles, and the ether driven off by gentle heating, or simply by standing the crucibles in a draught of air. In both

cases, the weights taken represent samples of ether-free antifoam, that is, " solid " or " dry " antifoam (Nos. 2 and 3 in Table I).

The amount of silica found in each material progressively decreased as more and more sediment was removed, first by standing and slow centrifugation and then by high-speed centrifugation which yielded particle-free, clear antifoam (Table I).

The figures are the best that could be obtained, and variability in the replicate analyses can be ascribed to the fact that the aliquots taken for analysis did not contain uniform amounts of amorphous silica which is added as a stabilizer.

These figures show that 64%, $\left(\frac{(7.3 - 2.6)}{7.3} \times 100 \right)$, of the total silica in the turbid antifoam is present as particulate material which can be removed as described.

A solution of antifoam without prior high-speed centrifugation and made up to a final concentration of 5% in a litre of ether would therefore contain 50 g. of antifoam which could be expected to remain on the sponges after the ether had been evaporated off. Of this, 45 g. is present as silicone, and 5 g. (0.5 g.% of the solution) is present as particulate material. This particulate sediment contains 75% silica, that is, 3.75 g. of particulate silica in the litre of original antifoam taken.

PARTICLE SIZING OF THE SEDIMENT.—The sediment contained 70–80% total silica. Examination in the x-ray spectrometer showed no evidence of any crystalline material, indicating that the silica is present in an amorphous form. Infra-red spectrophotometric analysis showed no significant concentrations of metals present. Particle sizing of four separate samples with the optical microscope using a 2 mm. oil immersion objective showed that 68, 59, 62, and 83% of the particles in the sediment were below 1 μ in diameter, and the remainder between 1 and 20 μ. The samples were in general heterogeneous in shape, and on many slides a considerable degree of aggregation of particles was evident, some aggregates ranging in size from 50 to 150 μ long and up to 80 μ wide (Fig. 1). This picture, together with Figs. 2–4, forms part of a representative collection of photographs of the " turbid antifoam " as prepared for use in the heart-lung apparatus and examined as smears. In addition to these, electron microscopic photographs show many particles of the order of 200 Å particle diameter.

PREPARATION OF ANTIFOAM XC-20033 FOR USE IN OPEN-HEART SURGERY

Without separate experimentation, it is not yet possible to say what concentration of antifoam solution is optimum for routine use in open-heart surgery, and work on this subject is urgently required. Reed and Kittle's study of 1959 is all that has been done in this respect thus far.

TABLE I
AMOUNT OF SiO₂ (% " DRY " WEIGHT) FOUND IN ANTIFOAM XC-20033 AT DIFFERENT STAGES OF PREPARATION

No.	Sample	% Total Silica (g. SiO$_2$/100 g. " Dry " Material Taken)
1	Antifoam XC-20033 Tin A (i)	54, 52, 41·5 (mean: 49·2)
	(ii)	52, 58·3 (mean: 55·2)
	Tin B	52·6, 47·4 (mean: 50)
2	Turbid antifoam (5%) (silicone + amorphous silica)	7·3
3	Clear antifoam (5%) (silicone only)	2·6
4	Sediment (amorphous silica only)	73, 80, 82·2 (mean: 78·4)

Concentrations of 5% (w/v) are used here, but this could almost certainly be reduced to avoid any possible concomitant dangers of globule emboli which have been described in many papers. It is also advisable to test new batches of antifoam materials for their antifoaming efficiency on closed circuits with ox blood over several hours bubbling and defoaming.

Until a pure commercial antifoam is available, the following procedure for the preparation of clear antifoam has been adopted in this laboratory.

Fifty grammes of antifoam is taken up in 300 ml. Analar ether and mixed well by vigorous stirring with a glass rod until all lumps of antifoam are broken up. The mixture is then allowed to stand for 24 hours. This removes the heavier silica particles by sedimentation, extracts the ether-soluble pure silicone material, and saves laborious centrifugation pro-
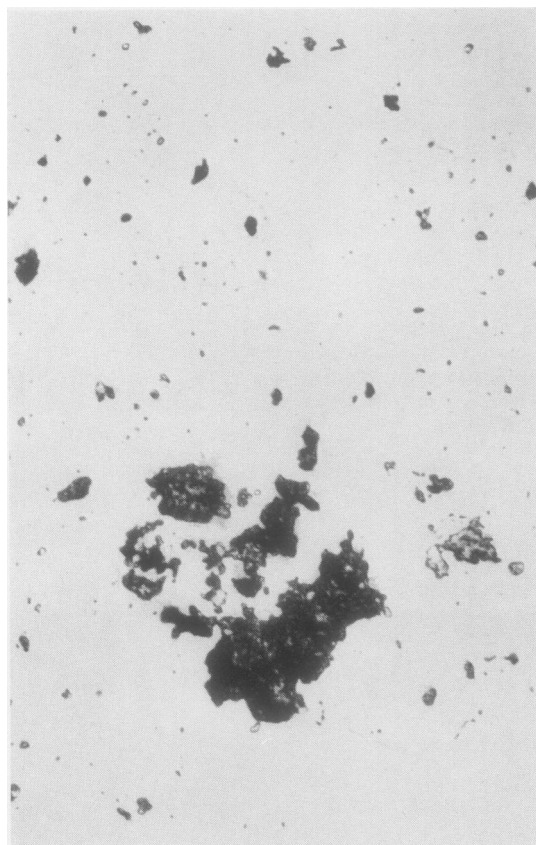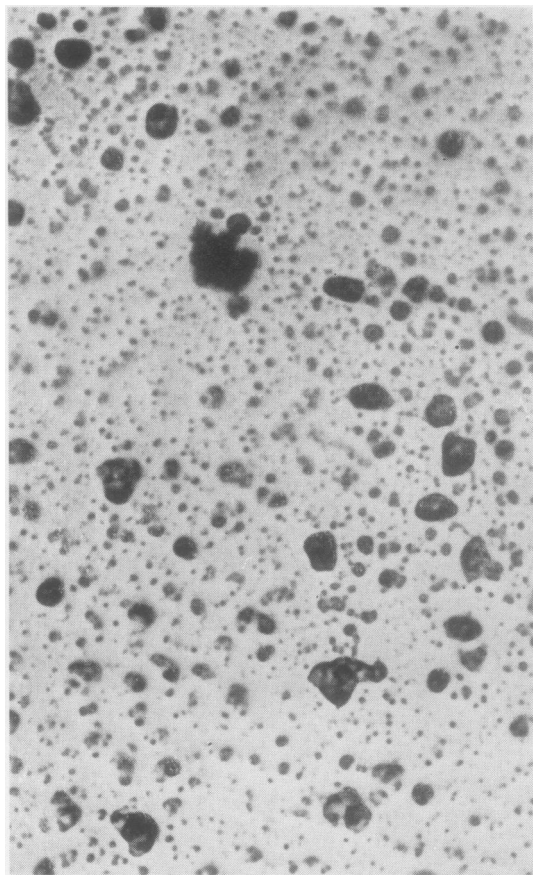

FIG. 2.—Smear preparation of a 5% antifoam solution showing particles of silica embedded in silicone after evaporation of ether.   ×320.   Impure antifoam preparations applied to sponges or meshes could be expected to give a similar picture.

FIG. 1.—Particles and very large aggregates of silica in a smear preparation of a 5% antifoam solution after evaporation of ether. ×160.   Large aggregate in lower centre is over 150 μ long and 80 μ wide.

cedures. Lumps of antifoam could be broken up more efficiently by means of a Waring blender or similar device, but the use of electricity in the presence of ether vapour could be hazardous. The supernatant liquid is decanted into a clean container, and the remaining antifoam material is washed by stirring with a further 200 ml. ether. The suspension-solution is allowed to stand for 24 hours, the supernatant again decanted, and the washing procedure repeated with another 200 ml. ether. Further standing is no longer necessary.

Two procedures were then followed during experimental work: the turbid, pooled supernatant material (pure silicone together with particulate matter in suspension) was centrifuged at 3,000 r.p.m. for 15 minutes, the clearer supernatants decanted, and filtered under air pressure through a Seitz filter capable of handling one litre volumes. In this way, it was hoped that perfectly clear solutions would be obtained, but the method became impractical because

of heavy clogging of the filter mats by the particulate material. Instead, the second method was followed. The pooled material was directly centrifuged at 9,000 to 10,000 r.p.m. in a high-speed refrigerated centrifuge for 10 minutes and the supernatants collected for use. This procedure provided a uniformly clear antifoam solution, and is now used as a routine method.

Using this method, about 600–700 ml. of clear, ethereal antifoam solution is collected, and the exact concentration determined by pipetting a known volume (1–5 ml.) into a weighed watch glass, completely evaporating the ether, and re-weighing the watch glass for its silicone material. More ether is added until a concentration of 5% (w/v) antifoam-ether, or whatever is required, is reached. This solution is then transferred to a screw-stoppered bottle and used for the treatment of the defoaming equipment.

More rapid methods of preparing clear antifoam solutions are conceivable, and could replace the time-consuming procedures of lengthy standing. For example, Soxhlet extraction of antifoam with ether
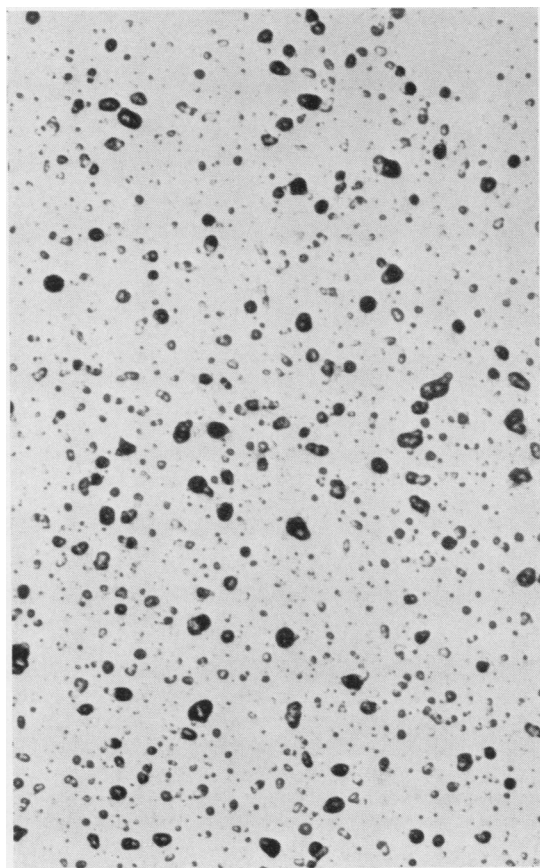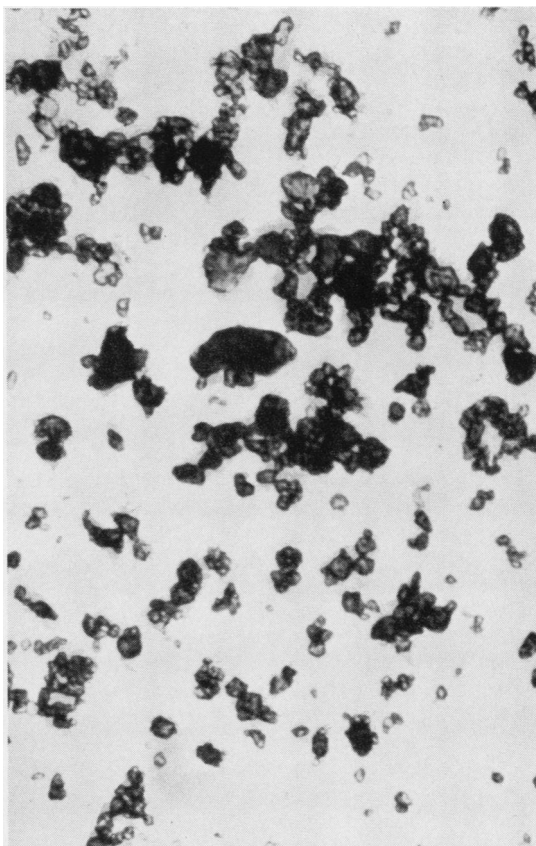

Fig. 4.—Smear preparation of a 5% antifoam solution. ×320.

would be a useful method requiring a few hours at the most. After this, high-speed centrifugation could be employed to clear the extracted material.

EXPERIMENTAL EVIDENCE OF SILICA SHOCK

Quartz of a defined range of particle diameter, if administered intravenously or parenterally, will normally produce a silicotic fibrosis. The intravenous injection of finely divided amorphous (colloidal) silica of particle-diameter range 200–500 Å (" aerosil " 99.8% SiO_2 from Degussa, Frankfurt am Main) results in three different responses: (1) A lethal dose (2 mg./kg. in rabbits) causes a shock-like death within 60 sec. of administration, so-called " silica-shock "; (2) high sublethal doses result in death after five to 10 hours; and (3) repeated low sublethal doses cause fibrosis in the liver and spleen.

Silica shock has been known since 1922–4 and 1932 from the work of Gye and Purdy (1922, 1924) and Kettle (1932), who described in detail the

Fig. 3.—Particles of silica in a smear preparation of a 5% antifoam solution. ×80.

pathological changes in the organs of animals after intravenous and parenteral injection of colloidal silica. These findings were later widely confirmed.

Gye and Purdy (1922) believed that death was due to massive clotting following damage to the vascular endothelium. However, not all necropsies on animals show such clotting, and it has been found here that during shock blood coagulation was slightly or not at all impaired when studied by conventional techniques, unless clotting occurs as a secondary phenomenon. " Silica emboli " as a cause of death were first precluded by Simson and Strachan in 1940. Then Modell and Salzman (1941) suggested that colloidal silica caused shock by constricting the pulmonary blood vessels, and four years later Filley, Hawley, and Wright (1945) reported a bronchoconstrictive action of colloidal silica in isolated, perfused guinea-pig lungs.

The work on silica shock carried out in this unit has shown that the lethal dose of aerosil when administered intravenously is 2.0 mg./kg. for rabbits and 13.6 mg./kg. for rats. Death in all cases was characteristic and took place within one to two minutes after injection. The symptoms preceding death showed certain resemblances to those associated with anaphylactic shock ; the animal became restless, cried out, became convulsed, made pedalling movements with the forelegs, developed rapid and deep respirations, lost reflexes, and died. The shock could be induced in guinea-pigs and mice as well as in the two species described. To a certain extent death could be prevented by the prior administration of antihistaminic substances (Harington, 1960), but these agents offered little hope of an explanation of the origins of the shock. The next observation, that silica shock could be totally prevented by prior administration of anticoagulants, heparin and Miradon (Scherag Co.), returned the problem to the province of blood coagulation, and the possibility that release of " contact factor " was involved (see review by Biggs and Macfarlane, 1953 ; Margolis, 1957, 1958), or some other agents with physiological activity, was investigated ; it was believed that such a phenomenon might explain certain of the aspects of death which are at present difficult to resolve. It has been well established that quartz and some silicates have a pronounced surface action on certain blood factors which *in vitro* lead to the release of highly active plasma kinins, with subsequent coagulation, smooth muscle contraction, and pain (Armstrong, Jepson, Keele, and Stewart, 1957 ; Margolis, 1957, 1958), but further work on this subject has excluded " contact factor " as a contributory cause. The powerful and immediate vasoconstriction obtained after the injection of colloidal silica into experimental animals is at present being examined in an effort to distinguish a possible physiological vasoconstriction from a mechanical embolism produced by the heavily hydrated submicroscopic particles which were used. Perfusion experiments using saline suggest that haematological factors are not directly implicated, though massive clotting might certainly be a secondary phenomenon in experimental animals receiving this type of silica.

Silica shock can be reasonably ascribed to a specific action of silica, since it does not occur with tungsten oxides, carbon, or silver of the same size (Harington and Sutton, 1961), nor did it occur with 12 other materials of particle diameter 200–600 Å injected intravenously by other workers.

It was at one time believed that pure antifoam would form a coat around the particulate matter when both were present, and in this way possibly prevent any surface activity of the silica. However, tests in the laboratory have shown that this is not the case, because the presence of antifoam in no way prevents such surface activity ; in fact, an increased amount of soluble silica is released after the action of the antifoam, but this is probably of no importance to the general picture.

DISCUSSION

POSSIBLE TOXIC QUALITIES OF ANTIFOAM MATERIALS.—This paper points out, for the first time, the toxic properties of the particulate silica added as a stabilizer to the commercial silicone preparations used as defoaming agents in open-heart surgery. As well as this hitherto unsuspected danger, there are at least 12 accounts in the literature referring to possible tissue damage caused by silicone emboli in humans and animals after perfusion experiments involving the use of antifoam substances, and it is felt that it is pertinent to review this aspect of the field.

The first real suspicion that some post-operative signs and symptoms of nervous tissue damage were occurring in experimental animals under intracardiac surgery was voiced by Giannelli, Molthan, Best, Dull, and Kirby in 1957, when they reported focal lesions in the brains of dogs that had undergone partial perfusions with bubble oxygenation. In the same year, Kirklin, Patrick, and Theye warned against the possible danger of embolism by particulate material or air entering the patient with arterial blood. There is little doubt that silicone materials in general are of relatively low immediate toxicity (Rowe, Spencer, and Bass, 1948 ; Barondes, Judge, Towne, and

Baxter, 1950; Cutting, 1952; Polemann and Froitzheim, 1953), and one study on an antifoam material supports this (Rosenbluth, Epstein, and Feldman, 1952). In 1958, Taylor reported that pulmonary collapse and haemorrhage had caused death in a large number of dogs which had been partially perfused with a bubble-oxygenator type of machine. Post-operative haemorrhage in particular was considered responsible for many of the deaths during the experimental surgery. Seven cases showed evidence of cerebral damage, and it was assumed that this damage had made a major contribution towards death. Histological examination of two of the brains showed areas of focal oedema and necrosis, having a widespread distribution and accompanied by death of nerve cells. Kirby in 1957 reported similar changes after a partial by-pass of two hours. Taylor had concluded that the histological appearance was consistent with that produced by multiple microscopic emboli rather than anoxia. He stated at that time that there were good grounds for the belief that excessive venous pressure or embolization from antifoam globules were not causative agents.

These observations were later continued and extended by Taylor and Cavanagh (1958), who found that, in 10 out of 13 dogs which had undergone experimental cardiopulmonary by-pass using a bubble oxygenator, multiple focal necroses were encountered in the cerebrum and cerebellum which were probably attributable to small emboli. The various possible sources of embolic material were discussed. Excluding fat emboli from the operative areas, the authors considered three likely sources of embolic material: fibrin formation, the presence of minute gaseous emboli, and the separation of antifoam globules after excessive application of antifoam. Silicone material could not be detected in the brains examined by the histological techniques used, the main difficulty being its non-staining properties, its solubility in lipid solvents, and its failure to deviate polarized light. Chemical analysis would probably have been necessary, together with micro-incineration of sections, in order to examine for the presence of particulate material.

Abrahams (1960) carried out histological examinations in the Department of Pathology, University of the Witwatersrand Medical School, on a number of dogs after intracardiac surgery during 1957 to 1959, and found material both of a globular nature (without staining properties) and of a particulate nature in sections of brain tissue. Deposits of non-staining globules were also detected in glomeruli of the kidneys.

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Electroencephalographic studies during by-pass using bubble oxygenation showed undesirable changes when compared to film oxygenation (Owens, Adams, Dawson, Lance, Sawyers, and Scott, 1958), and physiological disturbances in the blood-brain barrier were recorded by Hodges, Sellers, Story, Stanley, Torres, and Lillehei in the same year.

Recent evidence has left little doubt that the whole question of antifoam hazard requires careful, immediate, and responsible scrutiny. Antifoam infarcts have been produced in the brains of dogs by intra-arterial injection (Penry, Cordell, Johnston, and Netsky, 1959), and embolic lesions in the dog by the same route were reported by Reed and Kittle (1959), who in a very relevant paper advocated judicious care in the use of antifoam, and this warning is reflected in the publications of Hudson (1959), d'Abreu (1959), and Clowes (1960). One of the two most recent publications on antifoam hazards in intracardiac surgery is that of Yates, Cassie, Dark, Jack, and Riddell (1959), who identified antifoam emboli in the brains of dogs which had undergone total by-pass, and the second is the interesting study made in 1960 by Cassie, Riddell, and Yates, who found that antifoam emboli were invariably produced in dogs during by-pass with bubble oxygenation. Many of the animals suffered cerebral infarcts from these emboli, which were due to a proprietary defoaming agent; in addition, haemorrhage was a common cause of death. Concentrations as high as 20% antifoam in ether were used in these studies, and reductions in the amount used increased the survival rates of the animals and allowed them to recover consciousness more rapidly.

The amount of particulate silica must have been very considerable at 20% concentration (the present paper reports a concentration of 0.9 g. particulate material per 100 ml. ethereal solution of the antifoam used by these authors), and there is evidence in the illustrations of particles in suspension in the globules which had been detected in the tissues. Furthermore, their illustration (Fig. 8) of antifoam globules on glass which had been dipped in 20% antifoam in ether strongly suggests that it is particles which are visible and not globules. Photographs of clear solutions of antifoam on glass should be difficult to take because of the complete absence of material "landmarks." Their Fig. 8 may be compared with Fig. 3 of the present paper, which shows particles of silicious material found in antifoam. In addition, these authors report that the free colloidal silica in the antifoam is clearly less

"irritant" than when crystalline; this is not necessarily the case: amorphous silica can be as fibrogenic as crystalline forms (Gye and Purdy, 1922, 1924; and others).

The work of Yates *et al.* (1959) has recently been confirmed by Smith (1960), who on histological examination found focal cerebral lesions in 28 out of 39 dogs perfused by the Lillehei-DeWall system of by-pass. These lesions resulted from emboli derived from the 10% solution of silicone antifoam which was used; the renal glomeruli showed similar emboli. Antifoam emboli were detected in 26 out of the 28 brains showing focal histological lesions and in seven of the 11 brains in which such lesions were not detected. Of particular relevance to the present paper is Smith's frequent finding of amorphous debris in the globules of silicone found in the tissues. This debris is correctly described as amorphous silica of very fine particle size.

To complete the evidence at present available, a paper by Thomassen, Howbert, and Thompson (1960) reports the detection by phase microscopy and dark-field illumination of transparent, colourless emboli strongly suggestive of antifoam globules in tissues of humans and dogs exposed to antifoam materials.

Finally, mention should be made of the phenomenon of silica shock which has been described earlier in this paper. The presence in antifoam of colloidal silica of particle diameter 200 to 500 Å constitutes a danger which has not been hitherto considered in the use of antifoams containing particulate material. The experimental evidence carried out in this unit over the last two years confirms all earlier evidence that silica of this size has pronounced toxic effects, including clot formation, bronchoconstriction, vasoconstriction, and, in lower-than-lethal doses, possibly haemorrhage.

In the first 15 cases operated on by this heart-lung unit, using the DeWall oxygenator as originally described, the antifoam used was shown to contain a considerable amount of particulate matter, believed to be capable of doing harm to the tissues if allowed to enter the body freely. As single particles, most of this might pass through the capillaries; as aggregates, however, the particles might assume a general size of such magnitude that capillary occlusion could well occur. Both these hazards might possibly occur during by-pass, in which case particulate material would be totally trapped by the tissues of the patient.

The antifoam preparation which has been used over the past year is a clear solution, totally free of silica particles, and this has been associated with a much more trouble-free post-operative progress of patients subjected to open-heart surgery (Marchand, 1960). In addition, no reduction in the efficiency of the purified material has occurred at the concentration used. A new, clear proprietary antifoam is at present being tested for possible future use in intracardiac surgery.

SUMMARY

This paper is based upon a chemical examination of a proprietary antifoaming substance, XC-20033, extensively used in bubble oxygenators during intracardiac surgery. Particular attention has been paid to the size of the particles present in the material and to their silica content. As previously used, one litre of antifoam would contain 45 g. of silicone and 5 g. of particulate material, of which 3.75 g. would be in the form of amorphous, submicroscopic silica.

It is considered that the presence of this particulate material constitutes a danger during open-heart surgery where bubble oxygenators are used, due to the occlusion of capillaries by the larger particles, and, more important, to the toxic effect of submicroscopic particles of diameter 200 to 500 Å which are present in the antifoaming material. Silica of this size has been shown to be capable of producing a lethal shock or a delayed, possibly haemorrhagic condition in experimental animals.

There seems little doubt that, with the large number of highly effective silicone preparations available at the present time, a clear material could be produced for general use in intracardiac surgery to replace the ones in current use. Also, greater emphasis should be laid upon the statement made by the manufacturers that low concentrations of antifoam are required for efficient use, especially when in continuous contact with the oxygenated blood. Emergency barriers of antifoam of higher concentration or reserve sponges or meshes could be used as secondary lines of defence should any breakdown during by-pass occur.

problem, has accorded me great practical assistance and has offered criticism which has benefited the study very considerably.

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