THE EFFECTS OF INTRODUCING CERTAIN SUGGESTED SUBSTITUTES FOR TALC INTO THE PERITONEAL CAVITY AND INTO WOUNDS IN EXPERIMENTAL ANIMALS

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For many years talcum (a complex natural magnesium silicate) was the standard powder used for lubricating surgical gloves. A remarkably long time passed between the first use of talc for this purpose and the recognition by pathologists that it is a harmful substance. There is now a considerable literature on the subject,[1–19] of which Seelig, Verda and Kidd[7] give some 25 examples up to 1943. It has been established that the unabsorbable siliceous particles of talc cause a foreign body or giant cell reaction in tissues. The resulting granulomata may give rise to the most serious post-operative complications which entirely invalidate the benefits of surgery. Granulomata, pseudo-tuberculous reactions (leading to action based on a misdiagnosis), fistulæ, adhesions, sterility in females, and even acute abdominal crises causing death, have all been attributed with apparent justification to the evil effects of magnesium silicate. Experimental work with animals has shown that very small amounts of talc may cause severe damage in almost any cavity or tissue of the body, and that powder spilled in one part of the peritoneal cavity may be carried to other regions and there cause damage. Antopol[1] was perhaps the first to point out the dangers of talc, and Bethune[3] actually used it to produce fibrous obliteration of the pleural cavity, but its general use in surgery persisted. The attempt to substitute lycopodium for talc was abandoned when Erb[20] demonstrated that this substance was equally harmful. The undesirable effects of contamination of wounds with talc having been recognised, in recent years many attempts have been made to find a harmless and efficient substitute. The criteria for a desirable surgical glove powder have been outlined[21] and it is the aim of this paper to report the results of experimental trial of a number of such substitutes which are at present offered to the medical profession.

More serious than the accidental contamination of tissues with undesirable substances used as glove powders is the question of deliberate introduction of similar substances into wounds and cavities, frequently unwittingly on the part of the surgeon concerned, as a constituent part of chemotherapy applied in powder form—sulphonamides, antibiotics and mixtures of these. For this purpose wide use is made of a triturate of the sulphonamide with 5 per cent. magnesia mixed with penicillin, etc. (Dahl,[22] White[23]). Stearates have also been recommended for this purpose[24] because of their lubricity.

Finally, there is the question of introducing substances into tissues and cavities as a hæmostatic, or using them as a wound dressing. Such materials as Horsley's wax were long used to control hæmorrhage oozing

from bone, but granulomatous reactions and fistulæ as a result were not unknown. In America a whole group of "absorbable" hæmostatics has been developed and reported upon favourably. Fibrin foam with thrombin[25] has the advantage of being a biological product. Oxidised cellulose with thrombin[26] and gelatin with thrombin[27] have also been favourably received. In this country developments have occurred in the use of alginate (Blaine[28–31]). This substance, a phycocolloid, forms a continuous insoluble gel in the form of the calcium salt, whereas the sodium salt is water-soluble. These properties permit of its use in a great variety of ways, both medicinal and industrial. Varying proportions of the two salts result in substances which dissolve or are absorbed at differing rates depending upon the *p*H, vascularity and situation of the tissue or cavity where they are placed. Already a considerable literature is growing on the subject of the uses of alginates[32–36] in which it is suggested that this substance is harmless if used as a surgical glove powder, as a hæmostatic agent in many situations, or as an external dressing.

The substances investigated were (1) talc; (2), (3) and (4) three modified starches designated as starch (*a*), (*b*) and (*c*); (5) magnesia; (6) a mixture of magnesium carbonate and magnesium stearate; (7) magnesium stearate alone; (8) potassium bitartrate; (9) calcium and sodium alginate. All of these substances reach tissue wounds and cavities inadvertently or as a result of deliberate action during regularly executed therapeutic procedures.

Methods

The "commercial powders" were examined as received from the makers, other substances being of B.P. standard or equivalent standard obtained from reputable sources (e.g. talc, magnesia, bitartrate, stearate). The following tests were applied.

(1) An estimate of the mean particle size, before and after sterilising by the method recommended by the maker of the powder, or in an autoclave at 15 lb. pressure for 30 minutes, or with dry heat at 150° C. for 30 minutes.

(2) An estimate of lubricity by measuring in g. the weight necessary to be applied *via* a pulley to a block in order to overcome limiting friction. The block was enclosed in a portion of surgical glove attached with the inner surface of the glove facing outward, resting on a plane surface covered with a material which was selected from a number of fabrics, plastic, leather, rubber and other materials, treated and untreated skins, because it seemed in appearance, feel and other properties most similar to living skin. Dead human skin varies widely in its surface properties and can not easily be maintained in a constant state. Therefore it is not suitable for prolonged use which would require numerous fresh pieces of material of constant properties. The powders were applied in standard amount and by standard procedure between the opposed surfaces. Trials were made before and after autoclaving the powders.

(3) Samples of the powders selected from the depths of freshly opened packings as received were subjected to bacterial examination and again

after the recommended sterilising procedure. Incubation of samples proceeded in suitable media for 8 weeks, after which time any growth was subcultured and examined.

(4) A standard technique was applied to the examination of the effects of these substances upon living tissues. Rigorous aseptic technique was applied in the surgical work. Groups of 4 animals were used with each of the 9 powders. Kittens, rabbits, guinea-pigs, rats and mice were used. The larger animals were given a preliminary subcutaneous injection of atropine sulphate, all were anæsthetised with ether, and suitable areas of skin were shaved and washed with a solution of cetrimide. An attempt was made to produce (*a*) a standard 2-cm. incision through all layers of the skin of the back on the left side of the midline and (*b*) a standard laparotomy wound 2 cm. in length opening into the peritoneal cavity on the left side lateral to the recti and midway between the lower rib and the iliac crest, suturing being carried out carefully in layers with catgut for the peritoneum and muscle and fine silk for the skin. Into the skin wound was placed 10 mg. of powder, into the peritoneum 50 mg., in each case dry and tipped in loosely, and the wound closed. In the case of the mice the wounds were as small as could be conveniently made and less powder was used. The wound surface and the skin area, after suturing, were swabbed with the cetrimide solution and left undressed. Silk stitches were removed from skin after 10 days and the animals killed with coal gas after 6 to 9 weeks had elapsed. A careful post-mortem examination and report was made on each one, drawings of appearances were taken as necessary, and portions of tissue, etc. excised and examined by histological methods. The standard stain used was hæmatoxylin and eosin, but a polarising microscope was used on sections from all tissues in order to detect birefringent particles. An independent expert opinion was obtained on the appearance of most of the sections.

Results

The findings as to particle size and lubricity are summarised in Tables I and II respectively. Talc, as is well known, is a very fine powder, the mean particle size being the smallest of this series, but modified starch which approaches it in size is a much more even powder. Starch (*b*) is the most even of the three starches, the granules seeming to be largely unaffected by the process of hardening employed. The stearates have a

TABLE I

Particle size of powders in microns, after sterilisation

Substance	Mean	Range	Standard deviation	Mode
Talc	7·6	0·6 to 123·0	± 6·1	0·6
Starch (*a*)	10·1	1·2 to 19·5	± 1·4	8·5
(*b*)	11·1	2·4 to 19·5	± 1·4	11·0
(*c*)	11·3	2·4 to 27·0	± 1·4	11·0
Magnesia	16·1	2·4 to 134·0	± 6·3	6·1
Magnesium carbonate-stearate	30·3	2·4 to 244·0	±15·1	6·1
Potassium bitartrate	26·4	2·4 to 171·0	±11·0	6·1
Alginate	41·7	2·4 to 220·0	±16·0	30·5

TABLE II

LUBRICITY, EXPRESSED AS WEIGHT REQUIRED TO OVERCOME LIMITING FRICTION. APPEARANCE AND FEEL OF POWDERS

Substance	Before autoclaving	After autoclaving	Appearance and feel
	g.	g.	
Talc	107	125	same
Starch (*a*)	100	100	same
(*b*)	134	134	same
(*c*)	117	117	same
Magnesia	174	174	lumpy
Magnesium carbonate-stearate	93	93	lumpy
Magnesium stearate	125	—	solid
Potassium bitartrate	140	140	lumpy
Alginate	161	161	lumpy

greasy feel and melt with heat, which excludes them from use in a pure form where preliminary sterilisation is essential. This property probably accounts for an observed increase in particle size of the carbonate-stearate mixture after autoclaving. However, this powder retains its smooth feel and the "slipperiness" is not affected. No powder showed variation in the critical measure of limiting friction from sample to sample, and only talc was rendered less slippery by the process of sterilisation. No direct correlation exists between the particle size and the lubricity, other properties than size and shape of particles having an effect. Thus, neither magnesia nor potassium bitartrate is very slippery, both clump somewhat after autoclaving, and yet bitartrate is much more abrasive to the skin and to rubber gloves. Both alginate and the carbonate-stearate mixture form rather lumpy powders after autoclaving, but there is a marked difference in their lubricity. There is little difference in the particle size of the three modified starches tested, but some difference in lubricity.

TABLE III

STERILITY OF POWDERS BEFORE AND AFTER AUTOCLAVING (8 WEEKS GROWTH)

Substance	Before autoclaving	After autoclaving
Talc	sterile	sterile
Starch (*a*)	contaminated	sterile
(*b*)	sterile	sterile
(*c*)	contaminated	sterile
Magnesia	sterile	sterile
Magnesium carbonate and stearate	sterile	sterile
Magnesium stearate	contaminated	sterile
Potassium bitartrate	sterile	sterile
Alginate	contaminated	sterile

All these substances are capable of being sterilised by routine means: several of them are sterile in the raw state. Others are contaminated by streptothrix. From none of them were pathogenic organisms isolated. Nevertheless it is obvious that great care must be taken that no non-sterile substance reaches the tissues by the admixture of a non-sterile adjuvant to a chemotherapeutic powder.

The effect of the powders on the tissues of the skin and on the peritoneal cavity were assessed by applying the code shown in Table IV. The mean figure thus obtained from each group of 4 animals of one species is

TABLE IV

CODE APPLIED IN ASSESSMENT OF EFFECTS OF POWDERS ON SKIN WOUND AND PERITONEAL CAVITY OF ANIMALS

Skin	Peritoneum
0 = N.A.D.	0 = N.A.D.
1 = slight fibrosis	1 = omentum adherent to wound site only
2 = fibrosis or slight round-cell invasion	2 = as above plus fibrous tissue masses, "bloom" on spleen, etc.
3 = foreign body reaction—slight	3 = as above plus slight adhesions remote from site of wound, granulomata, etc.
4 = foreign body reaction—more severe, with crystals	4 = general and severe adhesions, marked foreign body reaction in organs, etc.

shown in Table V, together with the total score. Obviously the substance scoring the least total is the least harmful to living tissue in common laboratory animals, and therefore possibly, or even probably, least likely to be harmful in man. Examination with the polarising microscope revealed heavy contamination with doubly refractile particles in all tissues containing talc, in occasional tissues containing magnesia, and in tissues containing starch (*c*). Postelthwait *et al.*[18] describe and illustrate the granulomata which may be caused by this same preparation (starch *c*) and the curious doubly refractile particles which it contains. Alginate had a collagenous appearance and slightly affected the refractive powers. Sections from tissues contaminated with the other substances showed no evidence of refractile bodies being present.

TABLE V

MEAN EFFECTS OF SUBSTANCES ON SKIN WOUNDS AND PERITONEAL CAVITIES OF ANIMALS ASSESSED ACCORDING TO THE CODE SHOWN IN TABLE IV

Substance	Kitten		Rabbit		Guinea-pig		Rat		Mouse		Totals		Total (maximum 40)
	skin	peritoneum	skin	peritoneum	skin	peritoneum	skin	peritoneum	skin	peritoneum	skin	peritoneum	
Talc	4·0	4·0	2·0	4·0	4·0	4·0	4·0	4·0	2·0	4·0	16·0	20·0	36·0
Starch (*a*)	1·0	2·0	1·0	1·0	0·0	1·5	1·0	2·5	1·0	3·0	4·0	10·0	14·0
(*b*)	0·0	3·0	0·0	0·0	1·0	3·0	2·0	1·0	0·0	0·5	3·0	7·5	10·5
(*c*)	0·0	3·0	0·0	0·0	1·0	0·0	0·0	3·0	1·0	4·0	2·0	11·0	13·0
Magnesia	0·0	1·25	1·0	1·0	2·0	3·0	2·0	3·5	0·0	2·0	5·0	10·75	15·75
Magnesium stearate-carbonate	2·0	3·0	0·0	2·0	1·0	1·0	1·0	2·75	1·0	2·0	5·0	10·75	15·75
Magnesium stearate	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0
Potassium bitartrate	0·0	0·25	1·0	1·0	0·0	0·75	0·0	1·25	1·0	2·5	2·0	5·75	7·75
Alginate	1·0	3·0	4·0	2·0	1·0	3·25	1·0	3·0	1·0	2·0	8·0	13·25	21·25
Total	8·0	19·5	9·0	11·0	10·0	17·5	11·0	21·0	7·0	20·0	45·0	89·0	134·0

	Total	Skin	Peritoneum
Mean damage, per powder	14·88	5	9·88
Mean damage, per species	26·8	9	17·8

DISCUSSION

From this table it may be deduced that no substance is entirely harmless with the exception of stearate, which acts as a control for the other observations. This substance is precluded from being of practical importance by itself because it is frequently contaminated in the raw state and is melted by heat. It leaves a greasy appearance in the peritoneal cavity, but no evidence of inflammation other than a microscopical appearance of swelling of connective tissue cells. Furthermore, it appears

that the peritoneal cavity is a more sensitive indicator of irritation than is the skin, for each substance examined, except stearate which is harmless at both sites in all species. The skins of the 5 species exhibit a graded degree of sensitivity to the total insult offered them, the peritoneal cavities differ widely in response, but any one powdered substance may provoke a similar response in the skins of all species tested (talc is universally damaging, stearate is harmless) or a widely differing response in two species (alginate). Again, a similar response may be evoked in the peritoneal cavities of all species (talc and stearate) or a widely differing response in different species (starch *c*). Individual animals in any specific group varied little in their response to any given agent applied to either site. Small groups of animals are therefore a justifiable saving of expense in conducting such a screening test. In this test 180 animals were used.

Excluding talc as being universally damaging and stearate as unsuitable for sterilisation, it appears that bitartrate is the least harmful substance, which agrees with the findings of Seelig *et al.*[7] and Verda.[37] Unfortunately, as has been stated authoritatively, this substance tends to macerate the hands of the surgeon and to shorten the life of surgical gloves.[21] The latter consideration is not of prime importance, but the former may well be. In this test alginate powder proved damaging to a moderate extent in all species at both sites and accordingly may well be excluded from our choice. It must be stressed that no conclusion may be reached as to the use of alginate dressings and hæmostatic preparations. Magnesium oxide and carbonate-stearate mixture were likewise not free from adverse effects though a great improvement on talc. This leaves the modified starch powders which have been praised by Lee and Lehman,[12] Eberl, George, May and Henderson[38] and McQuiddy and Tollman.[39] There appears to be little to choose between them, but none of them is entirely harmless as frequently claimed. There is little information available as to the nature of starch (*a*), but starch (*b*) is a formaldehyde-treated selected starch, and starch (*c*) is described as a mixture of amylose and amylopectin which does not contain formaldehyde but does contain 1 per cent. of magnesia. In total damaging effect, starch (*b*) had slight advantages over the other starches and this improvement is evident in the findings in the peritoneal cavity, though in some species it was by no means harmless. It has been stated that the use of a formaldehyde-treated starch powder is completely safe in human beings.[39] Microphotographs of the appearances of tissues treated with talc and the starch powders, together with other findings, have been published. (Graham and Jenkins[40]).

Summary and Conclusions

1. Tests were made of the particle size, lubricity and sterility of a number of substances which have been advocated as lubricating powders for surgical gloves, or as adjuvants to chemotherapeutic powders used to increase their rate of flow, viz., talc, three separate modified starches, magnesia, magnesium carbonate with magnesium stearate, magnesium stearate alone, potassium bitartrate and alginate powder.

2. The effects of admitting these substances to the skin and peritoneum after sterilisation was determined in groups of animals of 5 species.

3. As a result of these tests and certain authoritative statements which have been published, it was concluded that modified starches appear to be the most practicable substitute for talc at present available, but that further effort to produce a substance which is entirely compatible with human tissue is needed.

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