A COMPARATIVE EVALUATION OF ABSORBABLE HAEMOSTATICS

By GEORGE BLAINE, M.D., L.R.C.P. & S., L.R.F.P.S.

An absorbable haemostatic is a material which acts as a haemostat but is subsequently itself absorbed in the tissues, leaving no trace. Such a material is of use in certain cases of haemorrhage which it is impossible or impractical to control by more direct methods.

Since haemostasis was at all times one of the primary aims of surgery, it is obvious that the search for such materials is of long standing. Study of the history of surgery readily confirms this view. Ambroise Paré (*egg yolk*), Perthe (*defibrinated blood*), Broca (*serum*), Cushing and Horsley (*muscle stamps*) are some of the illustrious names associated with the earlier absorbable haemostatics.

The impetus of the last Great War produced further such materials, *fibrin foam* (Bailey *et al.*, 1944), *oxidized cellulose* (Frantz *et al.*, 1944), *gelatin sponge* (Correll *et al.*, 1944) and *alginates* (Blaine, 1945) being developed during this period. Of these four substances the first three were developed in the United States, the last in Britain. Gelatin sponge is now also produced in this country as well as on the Continent.

Whilst clinically all four materials have their protagonists and critics, it is commonly agreed that their haemostatic effect is satisfactory. Opinions differ as to their times of absorption. A review of the relevant properties of absorbable haemostatics seems therefore not out of place.

TABLE I

ORIGIN OF CURRENTLY USED ABSORBABLE HAEMOSTATICS

<i>Fibrin</i>	..	Human or bovine blood fraction, whipped to a foam and treated with formalin.
<i>Oxidized cellulose</i>	..	Oxidation product of cellulose, introducing 10 to 12.5 per cent. COOH.
<i>Gelatin sponge</i>	..	High-grade gelatin whipped to a foam and freeze dried, with

the addition of minute quantities of formalin.

Alginate Extract of seaweed (*laminaria cloustonii*) forming alginic acid, the sodium salt of which instantly reacts with calcium ions making it possible to produce films, yarns, wool or gauze of varying calcium sodium content.

Biochemistry

In order to evaluate the *in vitro* action on blood of these materials, measurement of prothrombin times was undertaken. These tests yielded the results shown in Table 2 (overleaf).

Whilst *in vitro* tests of this nature are of interest, they are by no means free from error. *In vivo* haemostatic tests were therefore carried out, using the experimentally cut surface of the rabbit's liver as the testing field. These tests revealed that all four haemostatics were rapidly effective in controlling capillary haemorrhage from the liver. It was noteworthy, however, that gelatin sponge and fibrin foam, in particular, adhered instantly to the bleeding surface. This adhesion was maintained for at least three days. With oxidized cellulose and with alginates, somewhat firmer pressure had to be maintained to achieve this adhesion. In some cases the material slipped from its position, probably through friction, in course of the period of observation. As three days are sufficient for a considerable amount of wound organization to occur, it was not considered necessary to continue observation beyond this arbitrary time limit.

Why the materials tested have haemostatic properties is difficult to answer (with the exception of fibrin) on other than mechanical grounds. The fibrin-thrombin reaction is biological and obvious. An alginate material containing more sodium than calcium (modified or 'fast' alginate), being very sensitive to calcium ions (which produce instant clotting of the alginate complex),

TABLE 2

PROTHROMBIN TIMES

Method:

Blood is collected into 'Wintrobe' mixed oxalate, i.e. 1.2 mg. ammonium oxalate + 0.8 mg. potassium oxalate to 1 ml. of blood, 0.1 ml. of plasma is added to 0.1 ml. 1/50,000 solution of Stypven, 0.1 ml. M/40 calcium chloride is then added. Tubes are constantly observed for clotting.

The test is carried out in a water bath at 37° C.

Results:

1.	Plasma	+	Venom	+	CaCl ₂	Mean of 6 tests	..	26.7 sec.
2.	"	+	Calcium alg. wool	+	"	"	3 "	9.8 "
3.	"	+	Cotton wool	+	"	"	3 "	6 "
4.	"	+	Sodium penicillin	+	"	"	3 "	59 "
5.	"	+	Thrombin	+	"	"	3 "	6.8 "
6.	"	+	Algin acid	+	"	"	3 "	42 "
7.	"	+	Calcium alginate	+	"	"	3 "	13 "
8.	"	+	Sodium alginate	+	"	"	3 "	6.6 "
9.	"	+	Buckley's* powder	+	"	"	3 "	11.6 "
10.	"	+	Calcium penicillin	+	"	"	3 "	30 "
11.	"	+	Oxycellulose	+	"	"	3 "	10 "
12.	"	+	Gelatin sponge	..	..	..	..	23 "

Notes:

0.5 per cent. solutions of all powders were used except penicillin.

Penicillin solutions were 10,000 units per ml.

The fabrics were used 5 mgm. to 0.1 ml. of solution.

The clot with algin acid was very small, the complete gel took some further time to form.

The clots with calcium alginate powder, sodium alginate and Buckley's powder were very soft.

The clots with oxycellulose were soft, gelatinous—not a true clot. Colour turns black.

* Sodium alginate	1 gm.
Magnesium ox. lev.	0.1 gm.
Calcium penicillin	20,000 units

(From *Brit. Dental J.*, 1947, 82, 213)

might have this property in addition to its mechanical haemostatic action. Though for oxidized cellulose it was claimed that it possessed an affinity for haemoglobin, forming an actual chemical combination, we are on safer ground if we content ourselves with the mechanical effect of these substances, in providing a scaffolding in the meshes of which blood can clot normally and rapidly. The *in vitro* effect of these materials on thrombin, however, should be noted (Table 2); except oxidized cellulose none of the others inactivate this vital element of the clotting mechanism.

Effect on Antibiotics

Absorbable haemostatics and antibiotics, particularly penicillin and streptomycin, are often used in conjunction. It is essential that antibiotic activity should not be lessened by the use of a simultaneously implanted substance. Oxidized cellulose alone exerts an adverse effect; the other materials do not.

Sterilization

Fibrin foam and oxidized cellulose are sterilized chemically, formaldehyde, zephiran and chloroxylenol being satisfactory antiseptics for this purpose. Oxidized cellulose cannot be sterilized by heat; fibrin foam can be so treated, with certain precautions, using oil. Gelatin sponge is heat-sterilized by the makers, using special processes; re-sterilization by dry heat is possible but alters the absorption rate of the material. Alginates can be heat sterilized, either by autoclaving or by the application of dry heat.

Effect of Pathogenic Micro-organisms

As a rule absorbable haemostatics must be used in surgically clean sites. Being digestible materials, all are prone to be culture media for organisms. This property is in inverse ratio to the solubility of the product. Thus thoroughly formalinized fibrin foam, gelatin sponge or a high calcium, slowly absorbable alginate, do not lend themselves well to bacterial growth. This pro-

perty is perhaps most marked with alginates in the process of manufacture of which a cetrimide-like substance is used (cetyl pyridium bromide) which renders even the high sodium, rapidly absorbable material comparatively inimical to the growth of micro-organisms.

Tissue Reaction

Ample evidence is available on the behaviour of all absorbable haemostatics in animal tissues. Normally they are absorbed in the same way as a bloodclot derived from the extravasated blood of the same subject. This should be kept in mind, as it largely explains the variability of absorption rates in clinical experience.

Fibrin Foam.—According to the careful observations of Bailey and his colleagues (1944, 1945), fibrin foam is absorbed in about five weeks. After an early polymorphonuclear reaction (third to sixth day) a fibroblastic reaction develops (visible after the tenth day) and giant cells appear. After about two weeks the implant area is well organized, new blood vessels are forming and the round cell reaction, marked earlier, is subsiding. After about three weeks there is massive fibrous tissue reaction, with fibre formation and disappearance of the giant cells. At four to five weeks after implantation a fibrous scar only marks the site of the foreign body.

Oxidized Cellulose.—According to Frantz and Lattes (1945) small test pieces of oxidized cellulose gauze, not previously soaked in blood, were sometimes entirely absorbed in the subcutaneous tissue of the back of the rat as early as the fourth day. Used as an absorbable haemostatic, however, where the material would naturally be soaked in blood, the absorption rate was much longer. Tissue reaction was similar to that described above. At 24 days post-operatively there were still remnants of material in the biopsy specimens. At 30 days no oxidized cellulose could be found in test pieces.

The same authors, however, drew attention to the retarding effect on bone-healing caused by oxidized cellulose. This is probably due to the marked acidity of the material, which retards early callus formation. Some retardation of epithelialization was also noted; it is obvious that a material of a pH 3-4 is not suitable for the purpose of surface wound cover.

In marked contrast to Frantz's (1946) observations in whose opinion oxidized cellulose did not give rise to adhesions in the abdominal cavity in experimental animals, Dmytryk (1947) found that, used in the presence of traumatized peritoneum, massive adhesions followed its use.

In fact the same observations were made by me in respect of all absorbable haemostatics in experi-

mental conditions where the serosa was damaged. Dense adhesions formed whether fibrin, gelatin or alginates were used. The use of absorbable materials as tissue-isolators, however, falls outside the scope of this review.

Gelatin Sponge.—The tissue reaction to gelatin sponge has been fully described by Correll *et al.* (1945). It is in every respect similar to the reaction to fibrin foam.

Having recently re-investigated the tissue reaction to British-made gelatin sponge (Allen & Hanbury), these findings were, on the whole, corroborated. Figs. 1 and 2 show typical appearances in the rabbit.

None of the authors cited, however, make sufficient reference to causes of failure of absorption. Since clinical experience of the last few years has shown that absorbable haemostatics do not always absorb as they should, it is worth applying a little thought to the matter. If excess material is used in comparison to the absorptive capacity of the recipient area, cytological response becomes sluggish and, giving up the effort to absorb the super-abundant material, tissue elements proceed to encapsulate the implant.

If an absorbable haemostatic effectively arrested haemorrhage and subsequently lies in a tissue or tissue plane where reaction is minimal (as in a fascial plane), it will remain there, enveloped probably by a thin layer of fibrous tissue. Placed in a cavity with a different pH to that generally obtaining (e.g. the vagina at certain times of the menstrual cycle), non-absorption again results.

An over-large gelatin sponge implant left in the liver of a rabbit was found at four weeks post-operatively to show little sign of absorption and to be densely encapsulated. The entry of phagocytes into the central areas of the implant being thus prevented, no further absorption could be expected and the cystic tumour would have persisted.

Alginates.—The possibility of altering the constitution of an alginate material within physiological limits (i.e. from a material saturated with calcium and of slow absorption rate, to one in which sodium almost completely replaces calcium and the absorption rate is greatly increased) is an outstanding feature of this absorbable haemostatic.

Calcium alginate takes up to 12 weeks to be absorbed in most sites. The tissue reaction is similar to that seen with the other materials tested. After the early leucocytic reaction fibroplasia is usually marked without, however, much giant cell reaction. The final fibrosis is as with other absorbable haemostatics. The majority of histological sections taken between two and three months post-operatively revealed no sign of the alginate implant.

FIG. 1.—Gelatin sponge implant in the greater omentum of a rabbit at one week. Note the marked polymorphonuclear reaction.

FIG. 2.—Gelatin sponge implant in parietal peritoneal wall at 3 weeks. Only a few small 'ghost' remnants of the implant are visible; there is marked new blood-vessel formation.

Sodium : calcium alginate or modified 'fast' alginate presents a different picture. Ten days after implantation only minute remnants are found, and these with some difficulty, showing that the implant has been entirely absorbed. In experiments where there was minimal trauma and small implants only were employed, there was uneventful absorption within a few days.

Figs. 3 and 4 show what is to be expected in using an alginate material in stemming haemorrhage from a parenchymatous organ, such as the liver. A slice of hepatic tissue was resected from the inferior surface of the liver and the duodenum was slightly roughened by rubbing it with dry gauze. A piece of 'fast' alginate wool was placed on the bleeding surface and a biopsy specimen was taken one week post-operatively. This shows a marked polymorphonuclear reaction, without tendency to encapsulation; the adjacent liver tissue is normal and fragments of the alginate material are seen in course of absorption by phagocytes.

Other workers have carried out experimental

studies with alginates. Thus Frantz and Chenoweth (1948) declared alginates toxic and unsuitable for use in humans, based on a series of experiments in which nitrated alginates and alginate-aldehydes were used. These findings were surprising both in view of the obscurity of reasons why such alginate salts were used (the British material is based on the physiological salts of calcium and sodium) and why summary dismissal of favourable evidence was made in the author's summing up. Martin and Gosset (1949) and Dagradi (1949) dismiss the American findings as uncritical and the French authors in particular draw attention to the experimental techniques used which bore little relation to practical, surgical conditions. Martin and Gosset corroborated the absorption 'spectrum' of calcium alginate, producing almost identical histological findings to those described by me (Blaine, 1947). Dagradi (1949), on the other hand, whilst confirming the non-toxicity of alginates, has drawn attention to the differences in absorption time using calcium alginate.

FIG. 3.—Alginate (fast absorption rate) in experimental wound of liver. Mouse, 7 days postoperatively. The pledget of alginate is firmly wedged between the cut liver surface and the roughened duodenum. There is no tendency to encapsulation.

FIG. 4.—Higher magnification of the same section. Liver tissue in the region of the wound is healthy; fragments of alginate are seen surrounded by polymorphs and red blood cells. Fragments close to the liver are already undergoing absorption.

Both Martin and Gosset and Dagradi make the sensible point, hitherto hardly noted, that an absorbable haemostatic behaves similarly to an absorbable foreign body of physiological origin, such as a blood clot or bone fragment. The rates of absorption and wide variability of reactions to such autogenous materials are too well known to merit discussion. A small extravasate in muscle, for instance, absorbs quickly; a fibrinous exudate in the pleura does not.

Clinical Findings

After extensive experimental studies, therefore, absorbable haemostatics have now been in clinical use for more than five years. How do clinical results compare with these experimental findings?

Fibrin foam was the first of the current materials submitted to clinical trial. Developed at the Harvard Medical School, it found ready acceptance in most hospitals throughout the United States and for a time it reigned supreme. Although used in various branches of surgery, its main usefulness was in the surgery of the brain, where it proved invaluable.

Unfortunately fibrin foam is difficult to produce and for this reason more than any other it has been largely replaced.

Oxidized cellulose has been extensively used in

various branches of surgery. Reports during the first three years of its use were all favourable, with the exception of those concerning its use in bone surgery where it was found to retard healing. The fact that it interferes with antibiotic activity and with thrombin potency has also been mentioned.

Used in moderate amounts and where fast absorption is not necessary, it has proved to be a safe and sound haemostatic. In cases where too much material had been used, complications were avoided by removing the excess, a procedure worthy of adoption with all absorbable haemostatics in accessible sites.

As a case in point, Latta (1949) reported urethral blockage from unabsorbed oxidized cellulose after a prostatectomy. Anuria was overcome by irrigating the bladder which led to the expulsion of the unabsorbed mass of material, after which recovery was uneventful.

Gelatin sponge has also been used extensively. Its field of usefulness covers practically the whole range of surgery and there are many reports indicating its efficacy (Jenkins 1946, MacDonald *et al.* 1947). The same principles apply, of course, as with other absorbable haemostatics; if used in excess, absorption does not take place.

Until recently all the data on gelatin sponge

came from American sources. Now investigations have been carried out with British gelatin sponge (Blaine 1951, Lee 1951) which corroborated the American findings and, clinically, find gelatin sponge eminently suitable for use in prostatectomy, provided a meticulous technique is used. The ready adherence of the material to the denuded walls of the prostatic cavity is an important feature.

Alginates also have their protagonists in clinical surgery. According to Blaine, Bray and Hudson (1948) various alginate materials are useful in casualty surgery; Blockley (1947), Brown (1948) and Rumble (1949) found it of use in dental surgery; Gossett (1949) recommends it in general surgery, having used it with success in various cases including hepatectomies; Gough (1943) and Mullard (1948) have used it in blocking tuberculous bronchi and in arresting oozing after extrapleural pneumothorax operations; Joublin (1949) employed it with success in various branches of surgery, notably in ear, nose and throat work; Blaine and Oliver (1950) reported on its successful use in 84 neurosurgical cases; Blaine and Passe (1948) described its usefulness as a post-operative dressing after fenestration operations for otosclerosis; various Belgian surgeons reported (1949) on the wide usefulness of the material in gynaecology (reconstruction of vaginal wall) as well as in general surgery.

In order to evaluate the usefulness of the various compounds developed, the writer was able to persuade the manufacturers to carry out a survey on the use of alginates in British hospitals. This was carried out in 1948 and 1949 by my friend, the late Mr. W. W. H. Stansfield, who found that alginates were used in more than 70 hospitals, ranging over the whole field of surgery, and were found highly satisfactory in about 75 per cent. of cases. Criticisms from the remaining 25 per cent. were directed against its slow absorption or non-absorption, tendency to fistula formation and indifferent haemostatic effect. It was noted that most of the criticisms came in cases where alginates were used not only to control haemorrhage but also to fill dead spaces (as after perineal excision of the rectum) or where larger implants were used than could be logically expected to absorb.

For instance, an alginate wool implant was recovered from the dura of a patient one year after the operation in which it had been used to control haemorrhage from the longitudinal sinus. It arrested the torrential haemorrhage for which it was used, but having done so and lying in a completely dry and avascular field, it proceeded to encapsulation and presented at cranioplasty 12 months later as an encapsulated tumour. It had,

however, no deleterious effects on the patient. It was noteworthy that there was no tendency to fistula formation, nor did the implant become infected, although the case was originally one of osteomyelitis of the skull. This example illustrates the factors predisposing to non-absorption.

A critical assessment of absorbable haemostatics thus shows that we have today at least four materials of value at our disposal. Of these, the first two, fibrin foam and oxidized cellulose, can be ruled out as unpractical; the first for difficulties of production, the second on account of its dollar-origin and certain disadvantages described above. There remain gelatin sponge of British origin and alginates. Both have their protagonists and critics; both have their place in surgery. Gelatin sponge is more uniform in its reaction and on account of its ready adherence to bleeding surfaces is often easier to apply. In cases where it is not necessary to use a material of an absorption rate of under, say, one to two weeks, it may well be the material of choice. Alginates, on the other hand, have a wider 'spectrum' of use and have the advantage that they can be easily sterilized and re-sterilized.

There is scope for far more work on absorbable haemostatics of all kinds. Gelatin sponge can be modified within a certain range to produce materials of different absorption rates; alginates readily lend themselves to further adaptation in the light of surgical requirements.

It can be claimed, therefore, that absorbable haemostatics have come to stay and already form part of the modern surgical armamentarium. At the present moment no other material has yet entered the field to compete with gelatin sponge and alginates, but possibilities of new absorbable haemostatics have been shown to exist from within the range of plastics, and from polyvinyl alcohol compounds in particular. Here then lies a fruitful field for further work which will undoubtedly be of benefit to surgery.

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