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(54) SURGICAL SYNTHETIC RESIN MATERIAL

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 TUNG, of 250, Frankfurter Strasse 61,
 Darmstadt, Federal Republic of Germany, a
 Joint-Stock Company organised under the
 laws of the Federal Republic of Germany, do
 hereby declare the invention, for which we
 pray that a patent may be granted to us, and
 the method by which it is to be performed,
 to be particularly described in and by the fol-
 lowing statement:—

The present invention is concerned with a
 new and useful surgical synthetic resin
 material.

It is known that antibiotics, especially genta-
 mycin, are slowly liberated from synthetic
 resins based on polymethacrylates and/or poly-
 acrylates. A steep initial drop in the concen-
 tration, due to the liberation of the antibiotic
 from the outermost layers of the synthetic
 resin, is thereby followed by an almost con-
 stant rate of liberation which, however, does
 decrease very slowly over the course of a long
 period of time. These antibiotic-containing
 synthetic resins have hitherto been used as
 bone cements for fixing endoprostheses, for
 example total hip endoprostheses, or in the
 case of changing infected endoprostheses. For
 combating infection or for prophylactic pur-
 poses, antibiotics are added to the synthetic
 resin before the complete polymerisation there-
 of.

We have now found, surprisingly, that syn-
 thetic resins in the form of granulates or of
 small spheroids, represent carrier materials
 for antibiotics with special advantages which
 are of particular use as surgical synthetic resin
 materials.

Thus, according to the present invention,
 there is provided a surgical synthetic resin
 material, comprising a synthetic resin based
 on at least one methacrylate and/or acrylate
 and at least one antibiotic, the synthetic resin
 being in the form of hardened granules or
 spheroids with a diameter of 1 to 20 mm,
 and preferably of 5 to 15 mm.

The new agent according to the present in-

vention preferably consists essentially of a co-
 polymer of methyl methacrylate and methyl
 acrylate.

According to an especially advantageous
 embodiment of the present invention, the indi-
 vidual granules or spheroids are connected
 together at least partially by means of fila-
 ments or wires.

Surprisingly, with the use of the new agent
 according to the present invention, novel and
 unforeseeable effects can be achieved.

An especially important field of use is in
 bone surgery, especially in the treatment of
 osteomyelitis. A surgical material of the type
 according to the present invention was hither-
 to unknown, although antibiotics-containing
 polymers have already been frequently des-
 cribed. There known materials were always
 agents which slowly liberated an antibiotic or
 served to stabilise it. The new agent accord-
 ing to the present invention can be used for
 filling osteomyelitis cavities. Most surpris-
 ingly, connective tissue grows into the inter-
 stices between the individual synthetic resin
 particles. Thus, in spite of the presence of an
 infection, the material is incorporated as in
 aseptic medium. The new agent can also
 be used for the provision of an aseptic trans-
 plant site for a possible subsequent applica-
 tion of Malpighian layer tissue from the
 patient's own body. The new agent can also
 be used for the open filling of osteomyelitis
 cavities when a primary skin closure is not
 possible. The uppermost layer of the par-
 ticles can be subsequently removed and the
 underlying particles are already substantially
 enveloped by connective tissue so that a skin
 transplant is possible.

In several very successful operations, it has
 been shown that granulation tissue forms in
 wound cavities packed with the new agent, the
 synthetic resin particles being encapsulated
 in fine connective tissue. A reorganisation of
 the site is thus achieved, without alteration of
 the elasticity or stability of the bone. In the
 case of the previously known fillings of osteo-
 myelitic cavities, there have always been used

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plugs of synthetic resin material which can only replace the defect in the bone from the point of view of volume but which unfavourably influence the elasticity of the bone. A removal of these previously used bone cement plugs, which is sometimes necessary, is, of course, only possible with very great difficulty. In contradistinction thereto, the new agent according to the present invention can remain in the cavity. Due to the particular form of the new surgical material, the natural stress and stability properties of the bone and its load-bearing strength are not changed. The given particle size of the material provides optimum, new and hitherto unachievable effects. In particular, an optimum filling of bone cavities can be achieved, without any use of pressure. This, for example, represents a further special advantage in comparison with the use of plugs made from foamed synthetic resins. In the case of these latter known materials, there is also the danger that residual low molecular weight components can diffuse out and harm the patients.

Finally, a very special advantage of the new material according to the present invention is that, in contradistinction to the previously known plugging, an unhindered flow off of secretions is ensured; this is of special importance in operations of this type since not only blood but also puss from the regressing infection must be able to flow away after the operation.

Synthetic resin materials for surgical purposes based on at least one methacrylate and/or acrylate are, in principle, known. Thus, for example, a bone cement is well-known which, in a standard packing, comprises two packs, each containing about 40 g. of powder, and 2 ampoules, each containing 20 ml. of liquid. The powder is a fine pearl polymer (particle diameter $<30\mu$) of a methyl methacrylate-acrylate copolymer, about 0.5% dibenzoyl peroxide being added to the powder as catalyst. For the identification of the material, traces of chlorophyll can be polymerised in during the production thereof. An X-ray contrast agent, the powder can also contain, for example, zirconium dioxide. The associated liquid consists of monomeric methyl methacrylate to which is added about 0.7% dimethyl - *p* - toluidine as accelerator, as well as traces of hydroquinone as stabiliser. As a rule, this liquid is also coloured with traces of chlorophyll for identification purposes. The powder, which is preferably packed in polyethylene packs, can be sterilised with ethylene oxide. The liquid can be sterilized by filtration and placed into glass ampoules.

Upon mixing together 2 parts by weight of powder and 1 part by weight of liquid, the dibenzoyl peroxide reacts with the dimethyl-*p*-toluidine in the liquid, radical polymerisation thereby being initiated. The mixture is so adjusted that it can be used as a paste

after only about 1 minute. This paste remains kneadable for about 4 minutes and then begins to harden, with the evolution of heat. After 6 minutes, the polymerisation is substantially finished. During the elastic phase, forming takes place, for example by injection moulding or by other methods known and described in the literature for producing formed bodies or granulates from synthetic resins, so that the surgical synthetic resin material is obtained in the form of a granulate or in the form of spheroids which, in both cases, should have surface areas and particle diameters which are as uniform as possible.

As stated above, the particle diameter is from 1 to 20 mm. and preferably from 5 to 15 mm. However, for special uses, other particle sizes can also be employed. When filling large cavities and in the case of an intended subsequent removal, larger particle sizes of, for example, 15—16 mm. can be used. In the case of filling small cavities in which it is not intended subsequently to remove the material, comparatively small particle diameters are usually preferred, for example of about 5 mm. The granulate or the material in the form of spheroids, which is, as a rule, preferred, can not only be produced immediately before the operation but can also be made available in the finished form. Of course, care must always be taken to ensure absolute sterility. According to an especially preferred embodiment of the present invention, the particles are joined together by means of filaments or wires. This can, for example, be achieved by producing bored spheroids (pearls) or, so long as the material is still in a plastic state, stringing it like pearls on a filament or wire or forcing filaments into the material. As filaments, there can be used any desired surgical stitching materials or also high alloy steel wires, such as are used for bone surgery. An agent according to the present invention in this form has the advantage that it is easier to handle during an operation and, in the case of a reoperation, can more readily be removed again. An initially only temporary filling in the case of a provisional treatment is also now possible, in this manner, for the first time. Furthermore, the wires used are capable of X-ray contrast. This means that, for example, a possibly desired removal of the particles from the connective tissue site is simplified; a temporary introduction of the agent according to the present invention into a marrow cavity is also possible, for example, after removal of a marrow pin because of marrow cavity phlegmons.

For the production of the agent according to the present invention, at least one antibiotic is incorporated into the synthetic resin before complete hardening thereof. For this purpose, there can, in principle, be used all known antibiotics which are not damaged by the heat which arises during the course of the

hardening and which are liberated from the synthetic resin in the desired manner. Since, however, the polymerisation to give the small particles according to the present invention makes possible a comparatively large surface area and thus a better conducting away of the heat of polymerisation, this condition is not critical. In principle, all antibiotics can be used, individually or in the form of mixtures, which are substantially thermostable at the temperatures which arise during the course of the polymerisation. Thus, they should be able to withstand temperatures of about 60 to 80° C. without any significant loss of activity. Furthermore, the antibiotics should be chemically stable towards the synthetic resins. Their spectrum of activity preferably includes gram-positive and/or gram-negative causes of diseases. If possible, the causes of the disease should have a retarded resistance development with regard to the antibiotics used. From the large number of possible antibiotics, there may be mentioned, by way of example, erythromycin, lincomycin, clindamycin, (see J. Pharm. Sc., 62, 1106/1973), novobiocin, bacitracin, vancomycin, fusidic acid, rifampicin, the polymyxines, neomycin, kanamycin, kanendomycin, tobramycin, lividomycin, sisomycin, and the antibiotics known under the designations BB-K8, DKB and AHB-DKB (antibiotic BB-K8 is kanamycin acylated on the C₂-amino group with L - (-) - γ - amino - α - hydroxybutyric acid; antibiotic DKB is 3',4' - dideoxy - kanamycin B; and antibiotic AHB-DKB is 1 - N - {(S) - 4 - amino - 2 - hydroxybutyryl} - 3',4' - dideoxy-kanamycin B); gentamycin is especially suitable. The penicillins and cephalosporins and other macrolide antibiotics can also be used. The aminoglycoside antibiotics are especially preferred because of their broad anti-bacterial spectrum and of their heat stability.

Gentamycin is, for example, an aminoglycoside antibiotics which acts preponderantly bacterioidally against gram-positive and, in particular, against gram-negative micro-organisms. However, all these micro-organisms sustain a chronic osteomyelitis so that this antibiotic has already been used in the case of osteomyelitis with the utilisation of its local and systemic action. Furthermore, it is known that gentamycin is especially advantageously liberated from synthetic resins based on at least one methacrylate and/or acrylate. The very good water-solubility of this antibiotic clearly has a very advantageous effect on the diffusion thereof from the synthetic resin. Its good ability to diffuse enables, after an initially comparatively great decrease of concentration, an almost constant liberation of the antibiotic which decreases only very slowly over an extraordinarily long period of time. Thus, even after several months, a sufficient degree of protection is ensured. This is of great advantage in comparison with the pre-

viously used treatment for chronic osteomyelitis in which the antibiotic was administered by installation or by through drainage. The antibiotic must thereby act counter to the flow off of secretions from the cavity and the most remote branchings of the fistula system are not reached. A through drainage can, because of blockage of the drainage tube, as a rule only be maintained for a very limited period of time.

Neither the production of the surgical material, for example the hardening process, nor the physical properties of the synthetic resin material are to unfavourably influence the effectiveness of the antibiotic. Publications concerning the behaviour of gentamycin (gentamycin sulphate or gentamycin base) are already available. Details of such investigations are to be found, for example, in Langenbecks Archiv für Chirurgie, pages 169—212/1972 (pub. Springer Verlag, Berlin and Heidelberg). The investigations regarding the liberation of the antibiotic from the agents according to the present invention include concentration tests in serum, urine and drainage samples.

In comparison with the previous use of an antibiotic-containing bone cement, the new surgical material according to the present invention also has the advantage that the synthetic resin is already hardened before introduction into the body. Thus, there is no evolution of heat in the bone tissue due to the completion of polymerisation, which means that the operation can be carried out under much more gentle conditions and no additional damaging of the filling site, through which not very much blood flows, can arise. Because the synthetic resin is extracorporeally hardened, there is a reduced danger of residual monomers being liberated during the operation, so that a potential risk with regard to the heart-circulation system does not arise.

The amount of antibiotic to be added can be varied within wide limits and depends essentially upon the activity of the antibiotic. In general, the amount of antibiotic added is between 0.2 and 20% by weight, referred to the polymer. In the case of gentamycin, additions of, for example, between 1 and 5% by weight, calculated as gentamycin base, have proved to be especially useful. The other antibiotics are preferably also used in amounts of adequate anti-microbial activity. The most readily available commercial packs with still not completely polymerised synthetic resin can be added with, for example, 0.5 or 1 g. gentamycin per approximately 60 g. of polymer (40 g. of powder and 20 ml. liquid). However, other antibiotic additions or mixtures of antibiotics can also be chosen. For example, a substantially higher addition of antibiotic can be made if a comparatively small cavity is to be filled but, nevertheless, a particularly effective dose of antibiotic is to be introduced. Since a

possible change of the mechanical properties of the synthetic resin material does not play an important part in the case of the surgical material according to the present invention. the amount of antibiotic used can be determined solely from the therapeutic point of view. In the case of a change of the cause of the disease or of resistance to the incorporated antibiotic, the agent according to the present invention can easily be removed and possibly replaced by another one containing another antibiotic or several other antibiotics.

The new surgical material according to the present invention is outstandingly useful for the treatment of chronic osteomyelitis. In carrying out the operation, the whole of the necrotic bone substance or tissue is first removed from the wound cavity. The resultant cavity is then carefully filled with the agent according to the present invention or spheroids or granules present on filaments or wires are placed therein. Due to the dimensions of the particles of the agent according to the present invention, an optimum filling of the cavity is possible. The new material has proved to be outstandingly useful in numerous operations.

A very rapid drying up of the pus secretion is observed. Open cavities filled with the new agent according to the present invention appear to be completely non-irritated and show no manifestations of inflammation. As an expression of the freedom from infection, the particles are slowly enveloped by connective tissue. The site of the particles can, furthermore, be very readily monitored since the synthetic resin particles can clearly be recognised on a roentgenogram. Furthermore, osteoblastic growth and the formation of new bone tissue in the interstices between the synthetic resin particles are observed.

The agents according to the present invention can also be used for infection prophylaxis in the case of heavy contaminated, extensive wounds in soft tissue or in the case of wound zones in compound bone fractures, such as frequently occur in the case of accidents, in the sense that the agents can be used for a temporary filling of a potentially infected wound cavity with uncertain skin closure. It is thus possible, for the first time, locally to use antibiotics in depot form, i.e. directly on an infected or endangered site. Furthermore, the administration can be discontinued as desired or can be purposely repeated. In the case of comparatively large wounds, it is particularly simple to introduce particles which are joined together by filaments or wires since all the particles can be removed without trouble, merely by pulling one end of the filament or wire. In this way, there is provided a completely new method for the treatment of wounds with antibiotics.

The following Examples are given for the purpose of illustrating the present invention:—

Example 1.

40 g. of a sterile, fine pearly polymer (particle size $< 30\mu$, consisting of a copolymer of methyl methacrylate and methyl acrylate, which additionally contains 0.5% dibenzoyl peroxide, traces of chlorophyll and 15% zirconium dioxide as contrast agent, are well mixed with 0.5 g gentamycin sulphate. The powder obtained is then mixed with 20 ml. of a liquid which consists of monomeric methyl methacrylate with an addition of about 0.7% dimethyl-*p*-toluidine and about 0.006% hydroquinone. The paste obtained after thorough mixing is then injection moulded to give spheroids with a diameter of about 7 mm. After about 6 minutes, the particles are hardened. If desired, the particles can be sterilised, for example, by treatment with gaseous ethylene oxide. The spheroids thus obtained can then be used for filling osteomyelitic cavities.

Example 2.

Spheroids with a diameter of about 7–10 mm. are produced in a manner analogous to that described in Example 1. 1 g. gentamycin sulphate is added per 60 g. of polymer. Before complete hardening, the particles obtained are strung like pearls, at a distance apart of about 2 mm., on to a filament, for example surgical, high-alloy steel wire, with a diameter of about 0.1 mm. When used for filling osteomyelitic cavities, the "string of pearls" can be cut off at any desired length.

Example 3.

A granulate with an average particle size of 6 to 8 mm. is produced in a manner analogous to that described in Example 1, 0.5 g. erythromycin and 1 g. neomycin being added before the polymerisation. The product obtained is used for filling osteomyelitic cavities.

Example 4.

40 g. of a pearl polymer are mixed with 2 g. tobramycin (referred to as base) in a manner analogous to that described in Example 1, polymerisation taking place after the addition of 20 ml. of the monomer-containing liquid. Spheroids with a diameter of 12 to 16 mm. are then produced by injection moulding. These can then be drawn on to a pliant surgical wire in a manner analogous to that described in Example 2, which simplifies handling during an operation.

Example 5.

Synthetic resin spheroids with a diameter of 8 to 12 mm. are produced by injection moulding in a manner analogous to that described in Example 1. Before the polymerisation, 40 g. of the pearl polymer are mixed with 4 g. lividomycin (referred to as base). The product obtained is used for filling osteomyelitic cavities.

Example 6.

A surgical material is produced in a manner analogous to that described in Example 3 except that 0.5 g. lincomycin is used instead of the erythromycin.

WHAT WE CLAIM IS:—

1. A surgical synthetic resin material, comprising a synthetic resin based on at least one methacrylate and/or acrylate and at least one antibiotic, the synthetic resin being in the form of hardened granules or spheroids with a diameter of 1 to 20 mm.

2. Material according to claim 1, wherein the granules or spheroids have a diameter of 5 to 15 mm.

3. Material according to claim 1 or 2, wherein the synthetic resin is a copolymer of methyl acrylate and methyl methacrylate.

4. Material according to any of the preceding claims, wherein the antibiotic is an aminoglycoside antibiotic and/or a macrolide antibiotic.

5. Material according to any of claims 1 to 3, wherein the antibiotic is erythromycin, lincomycin, clindamycin, novobiocin, bacitracin, vancomycin, fusidic acid, rifampicin, a polymyxine, neomycin, kanamycin, kanandomycin, tobramycin, lividomycin, sisomycin, antibiotic BB—K8, antibiotic DKB, antibiotic AHB—DKB, gentamycin, a penicillin and/or a cephalosporin.

6. Material according to any of the preceding claims, wherein the content of antibiotics is between 0.2 and 20% by weight, referred to the polymer.

7. Material according to claim 6, wherein, in the case of gentamycin, the content thereof is between 1 and 5% by weight.

8. Material according to any of the preceding claims, wherein the granules or spheroids are joined together at least partially by filaments or wires.

9. Surgical synthetic resin material accord-

ing to claim 1, substantially as hereinbefore described and exemplified.

10. Process for the production of a material according to claim 1, wherein at least one antibiotic is added to a synthetic resin based on at least one acrylate and/or methacrylate, before complete hardening thereof, the mixture obtained is formed into granules or spheroids with a diameter of 1 to 20 mm. and thereafter completely hardened.

11. Process according to claim 10, wherein the mixture is formed into granules or spheroids with a diameter of 5 to 15 mm.

12. Process according to claim 10 or 11, wherein the resin, prior to hardening is in the form of a pearl polymer with a particle diameter of $<30\mu$.

13. Process according to any of claims 10 to 12, wherein the polymer is hardened by reaction with monomeric methyl methacrylate.

14. Process according to claim 13, wherein the hardening is catalysed by dibenzoyl peroxide.

15. Process according to claim 14, wherein the hardening is accelerated by dimethyl-*p*-toluidine.

16. Process according to any of claims 10 to 15, wherein the antibiotic-containing resin is, after the formation of granules or spheroids, strung on to filaments or wires.

17. Process for the production of a material according to claim 1, substantially as hereinbefore described and exemplified.

18. Material according to claim 1, whenever produced by the method according to any of claims 10 to 17.

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Example 6.

A surgical material is produced in a manner analogous to that described in Example 3 except that 0.5 g. lincomycin is used instead of the erythromycin.

WHAT WE CLAIM IS:—

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2. Material according to claim 1, wherein the granules or spheroids have a diameter of 5 to 15 mm.
3. Material according to claim 1 or 2, wherein the synthetic resin is a copolymer of methyl acrylate and methyl methacrylate.
4. Material according to any of the preceding claims, wherein the antibiotic is an aminoglycoside antibiotic and/or a macrolide antibiotic.
5. Material according to any of claims 1 to 3, wherein the antibiotic is erythromycin, lincomycin, clindamycin, novobiocin, bacitracin, vancomycin, fusidic acid, rifampicin, a polymyxine, neomycin, kanamycin, kanendomycin, tobramycin, lividomycin, sisomycin, antibiotic BB—K8, antibiotic DKB, antibiotic AHB—DKB, gentamycin, a penicillin and/or a cephalosporin.
6. Material according to any of the preceding claims, wherein the content of antibiotics is between 0.2 and 20% by weight, referred to the polymer.
7. Material according to claim 6, wherein, in the case of gentamycin, the content thereof is between 1 and 5% by weight.
8. Material according to any of the preceding claims, wherein the granules or spheroids are joined together at least partially by filaments or wires.
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14. Process according to claim 13, wherein the hardening is catalysed by dibenzoyl peroxide.

15. Process according to claim 14, wherein the hardening is accelerated by dimethyl-*p*-toluidine.

16. Process according to any of claims 10 to 15, wherein the antibiotic-containing resin is, after the formation of granules or spheroids, strung on to filaments or wires.

17. Process for the production of a material according to claim 1, substantially as hereinbefore described and exemplified.

18. Material according to claim 1, whenever produced by the method according to any of claims 10 to 17.

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