GRAMICIDIN S

IT is now well known that Dubos and his co-laborators in America (see, among other papers by these workers, R. J. Dubos and R. D. Hotchkiss, *J. Exp. Med.*, **73**, 629; 1941) obtained from soil, sewage, manure and cheese, several species of aerobic, sporulating bacilli which are antagonistic to unrelated organisms, and that they recovered from these organisms an alcohol-soluble, water-insoluble fraction called tyrothricin, which kills many Gram-positive and Gram-negative organisms. From tyrothricin they isolated two crystalline polypeptides—gramicidin and tyrocidine. Tyrothricin is unsuitable for systemic administration (*Brit. Med. J.*, **122**, Jan. 27, 1945), but it is a powerful local antiseptic and has been used for the treatment of wounds, affections of the eye, nose and throat, empyema, certain skin affections and other conditions not requiring parenteral administration. It is now marketed by Messrs. Sharp and Dohme, Ltd., Mulford Biological Laboratories, Hoddesdon, Herts, who issue a booklet on its history and use, with a useful bibliography about it.

Russian workers (*Nature*, **154**, 703, Dec. 2, 1944; *Lancet*, **715**, Dec. 2, 1944) now report the discovery of another substance of the same kind as the American gramicidin. Prof. G. F. Gause and M. G. Brazhnikova, of the Moscow Institute of Tropical Medicine, report on their search, during 1942, among several hundreds of strains of bacteria from Russian soils for an organism similar to that discovered by Dubos and his collaborators. They often noted action antagonistic to bacteria in their cultures, but only one organism, isolated from garden soil, was remarkably effective. This belonged to the *Bacillus brevis* group and was similar to, but not entirely the same as, the one isolated by Dubos and Hotchkiss (*loc. cit.*). It produced, however, an antibacterial principle which is entirely different from that described by Dubos and his collaborators. This principle readily crystallized out when an alcoholic extract of the acid precipitate of the bacterial culture was poured on to a watch-glass, and it never occurred with the tyrothricin described by the American workers. The Russian authors regard this gramicidin as a new substance, different from other known crystalline polypeptides produced by aerobic sporulating bacteria. They call it 'gramicidin S'. Its antibacterial action against eighteen different strains of *Staphylococcus aureus*, ten strains of *Streptococcus* and against *Diplococcus pneumoniae*, *Clostridium welchii* and *C. histolyticum* is described by Gause and Brazhnikova. Comparison of it with tyrothricin showed that gramicidin S was rather more efficient in killing staphylococci, while tyrothricin killed streptococci and pneumococci more effectively; and gramicidin S was the less selective of the two. On the other hand, while tyrothricin is not effective against any of the Gram-negative organisms studied, as Dubos and Hotchkiss (*loc. cit.*) also found, gramicidin S prevents the growth of and kills "many varieties" of Gram-negative organisms, including *B. proteus vulgaris* and *Bact. coli*, which are common in infected wounds. The former is resistant to many antiseptics including penicillin.

At the same time, gramicidin S is very stable and is not more toxic than tyrothricin, the lethal dose (L.D.₅₀) for white rats being almost the same. Its antibacterial activity is not destroyed by autoclaving, nor do solutions of it used clinically interfere with

the activity of leucocytes. Treatment by the Russian workers of lacerated wounds of guinea pigs infected with *Cl. welchii* showed that the mortality of the animals thus treated was 5 per cent, while that of untreated ones was 53 per cent. When wounds of white rats were infected with garden soil, 100 per cent of the rats died, whereas, when such wounds were treated with gramicidin S, only 40 per cent died.

In the *Lancet* (*loc. cit.*) the chemistry of gramicidin S is discussed by A. N. Belozersky and T. S. Passhina and its clinical use is described by Prof. P. G. Sergiev, vice-president of the Medical Research Council of the U.S.S.R. Sergiev describes the results of treatment with gramicidin S of three hundred cases of gunshot wounds of soft tissue, severe burns, abscesses and anaerobic infections. The disappearance of necrotic tissue and appearance of granulations and epithelialization were very rapid. Gramicidin S was also useful for preparing wound surfaces for skin-grafting and for the treatment of empyema, peritonitis and impetigo.

Cytologists will be interested in the statement, in the article by Gause and Brazhnikova, that L. Levinson, of the University of Moscow, claims that gramicidin S favours regeneration of wound tissues and especially "the high nucleic acid content of the cells". If this means that the nucleic acid content of tissue cells is increased, this effect of gramicidin S merits further investigation in the light of E. Stedman's view, discussed in a recent article on the chemistry of cell nuclei (*Edin. Med. J.*, **51**, 353; 1944), that nucleic acid exists in nuclei in salt-like combination with histone and that diminution of histone from any cause might set free nucleic acid, which, by combining with chromosomin, might form a self-reproducing enzymic system analogous to the viruses with the result that, when growth reached a certain stage, mitosis would follow. Stedman suggests that histone may regulate mitosis (see also E. Stedman and E. Stedman, *Nature*, **152**, 566; 1943) and that the decrease of histone below a certain level may in this way render a cell malignant. The origin of histone is not known, but Stedman suggests that the lymphoid tissue may supply it; the nuclei of lymphocytes contain a high percentage of histone and the accumulation of lymphocytes around tumours may represent an attempt to remedy the deficiency of histone which is causing the malignancy. If this conception is correct, the confirmation of Levinson's statement that the cells of tissues treated with gramicidin S have a high nucleic acid content is desirable. For it is conceivable that the reported beneficial effect of gramicidin S upon regeneration of tissues may be due to an increase of nucleic acid caused by gramicidin S, with the result that more is present than the available histone can absorb, so that, as Stedman suggests, the excess combines with chromosomin, and cell divisions, that is, cell proliferation, follow. A further result is, however, conceivable. If gramicidin S treatment were sufficiently prolonged, some cells might be started off on a career of malignancy, especially if other factors were already reducing the available histone. It seems unlikely that gramicidin S itself could reduce the histone, but the possibility needs investigation. If, on the other hand, it could increase the histone, it might prove useful for the treatment of malignancy. The possibility that the American gramicidin and tyrocidine may have similar effects is also worth study. Whether similar effects can be exerted by other bacterial and perhaps fungal products can only be answered by the cytologist.

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