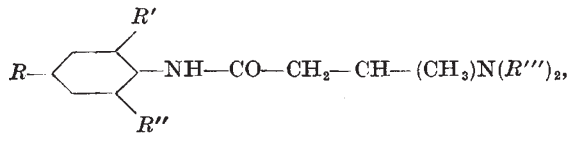
A New Type of Local Anæsthetic

Einhorn and Oppenheimer[1] more than fifty years ago synthesized a powerful local anæsthetic ('Nirvanin', the methyl ester of 3-diethylaminoacetylamino-6-hydroxybenzoic acid). Loefgren[2] prepared a similar compound ('Xylocain', 2-diethylaminoacetylamino-1-3-dimethylbenzene). Since this pioneer work in the field of local anæsthetics, many hundreds of effective compounds have been synthesized and tested; for a literature review on the subject, see Buechi, "Die Entwicklung der Arzneimittelforschung auf dem Gebiet der Lokalanaesthetica"[3].

A new series of compounds[4] of the type



where R = H or alkoxy, R' = H, CH_3 or alkoxy, R'' = H or CH_3, R''' = CH_3 or C_2H_5, has been prepared and shows marked local anæsthetic activity. One member of this series (R = OC_2H_5, R' and R'' = H, R''' = C_2H_5) was more active in guinea pigs than procaine and showed about half the toxicity in acute toxicity tests on mice. The other members prepared to date show approximately similar pharmacological properties to procaine, although their acute toxicity varies widely. Where R = H, R' and R'' = CH_3, R''' = C_2H_5 the toxicity in mice rises to about twenty times that of procaine.

Early attempts were made to synthesize the series from β-brombutyric anilide and dialkyl amines but resulted only in the formation of the anilide of crotonic acid. Treatment of this anilide, however, with excess amine under pressure gave the required substances in good yield.

Treatment of these β-dialkylaminobutyric anilides with concentrated hydrochloric acid yielded the corresponding aniline hydrochlorides and β-dialkylaminobutyric acid, thus establishing the position of addition of the amino group.

Full details of the chemistry and pharmacology of the series will be published elsewhere in due course.

Emil Hofstetter

Edward Geistlich and Sons, Ltd.,
Pharmaceutical Department,
Wolhusen, Lucerne.
June 4.

[1] *Annalen*, **311**, 155 (1900).
[2] *Arkiv Kemi Mineral. Geol.*, **22**, A, No. 18 (1946).
[3] *Arzneimittelforschung*, **2**, 1, 65 and 114 (1952).
[4] Patents pending.

Sepsis and Cortisone

That cortisone is able to suppress the inflammatory reaction irrespective of the nature of the causative agent is now a generally accepted fact. The site at which it is able to exert this effect remains uncertain; but it has recently been shown that cortisone can prevent or nullify an increase in capillary permeability[1], and that its administration is associated with an increase of arteriolar tone[2]. The latter authors consider that these two vascular effects are the most significant factors in the modification of the inflammatory processes.

In order to ascertain whether the effects of cortisone in acute inflammation would be consistent with such a view, we have investigated its influence in pyogenic infection. Eight rabbits were given an intracutaneous injection of 0·1 ml. of a 24-hr. broth culture of a coagulase-positive staphylococcus. Five of the rabbits received intramuscular injections of 10 mgm. cortisone acetate daily during the period of the experiment (commencing 24 hr. before infection) and three animals served as controls. The rabbits were killed on the fourth day after infection; the affected area of skin and subcutaneous tissue was excised, and serial paraffin sections were cut and examined.

There was a marked difference between the appearance of the resulting lesions in the test and control animals, those receiving cortisone showing a sharply demarcated chancroid nodule, in contrast to the less circumscribed fluctuant lesion exhibited by the control. The most striking feature observed, however, was the absence in the cortisone-treated animal of the normal polymorphonuclear infiltration and associated tissue necrosis, which was replaced by a dense mononuclear infiltration with minimal tissue destruction. An additional finding of considerable significance was the complete absence of organisms in the lesions of the test rabbits, whereas all control animals showed their presence in large numbers.

Our findings suggest that the suppression of the inflammatory reaction enables the organisms to disseminate rapidly, as has been observed by Lewis[3] and Antopol[4]. This dispersion from a small focus might be responsible for the severe infections described by Seyle[5] and by Gledhill and Rees[6] in animals treated with cortisone.

Two possible explanations can be advanced for failure to localize the infection: either no inflammatory fibrin barrier is formed and the bacteria are carried away by lymphatic flow, as suggested by Seyle[5], or changes at the vessel wall arrest leucocytic diapedesis and so prevent phagocytosis. Both these factors are probably at work. The mononuclear infiltration, not being entirely dependent upon diapedesis, arises through proliferation or migration in the adjacent tissues.

The absence of necrosis in the cortisone-treated lesions may be attributed to the absence of polymorphonuclears and of exudate containing proteolytic enzymes.

All the above effects of cortisone are more readily and simply explained by an interference with the vascular phenomena of inflammation, as suggested by Ashton and Cook[2], than by postulating its intervention at some other stage. This view is supported by the observations of Moon and Tershakovec[7], who have shown that cortisone does not effect the margination of leucocytes in an inflammatory lesion.

Charles Cook
Charles Smith

Institute of Ophthalmology
(University of London),
Judd Street,
London, W.C.1.
Aug. 27.

[1] Cook, C., and MacDonald, R. K., *Brit. J. Ophthal.*, **35**, 730 (1951).
[2] Ashton, N., and Cook, C., *Brit. J. Exp. Path.*, **33**, 445 (1952).
[3] Lewis, B. H., *J. Clin. Invest.*, **30**, 656 (1951).
[4] Antopol, W., *Amer. J. Path.*, **27**, 703 (1951).
[5] Seyle, H., *Canad. Med. J. Assoc.*, **64**, 489 (1951).
[6] Gledhill, A. W., and Rees, R. J. W., *Brit. J. Exp. Path.*, **33**, 183 (1952).
[7] Moon, V. H., and Tershakovec, *Proc. Soc. Exp. Biol. Med.*, **79**, 63 (1952).