treatment and to see the early manifestations of those diseases which eventually require admission of patients to hospital. This kind of training will be easier when more university departments of general practice and teaching health centres are in existence, and the report says that it is important that the student should observe general practice as a vocational opportunity for himself.

The G.M.C. suggests that opportunities for special study should be offered during the undergraduate period when certain subjects can be pursued in greater depth. Such experience, if carefully planned, may well have an educational value out of proportion to the limited scope of the project which is undertaken. Elective periods of study, involvement of students in research projects, or an additional year of study for an honours degree are all means of achieving this end. Interdisciplinary teaching should be encouraged throughout the curriculum, for it helps to break down departmental barriers, though the report points out that it is expensive in teaching time. When teachers from several disciplines unite to demonstrate the many-sided aspects of a chosen topic the experience can be most stimulating. Examinations should be geared to the curriculum of a particular medical school, and in addition special weight should be given to the student's record during the course. The G.M.C. recommends that a system of continuous assessment should be set up and maintained for this purpose.

The preregistration year has run into a good deal of criticism since it was instituted in 1953, the criticism coming mainly from the young people who have passed through it. The B.M.A.'s evidence expressed this, and the G.M.C. doubtless heard it from other sources as well. The main trouble is that routine duties are too often overwhelming, while opportunity for further education, let alone the deliberate provision of it, has been neglected. In the upshot the good habits of study and reflection, as the report says, "can be irrecoverably dissipated in a year of unresting labour." The G.M.C. makes a number of detailed proposals to counter this unhappy state of affairs, and they deserve to be set out in detail:

"(*a*) Posts should be in general hospitals with adequate laboratories for clinical investigation, radiological departments, and a working library.

"(*b*) Each preregistration post should be in the charge of a chief, or chiefs, who should each have not less that four consultant sessions per week in the hospital and should be directly responsible for the training of the holders of preregistration posts.

"(*c*) The non-consultant staff of each hospital department providing preregistration posts should include at least one senior registrar or, if not, one or more registrars in residence.

"(*d*) The responsibility of the holder of each preregistration post should be limited to that number of beds which allows him adequate time for his further education, and sufficient free time. The number should normally not exceed 30 beds, some of which should be for acute cases.

"(*e*) The educational nature of the post should be fully understood and accepted by all concerned, and the student should be allowed at least six hours weekly for educational purposes, apart from his free time. There should be an educational programme for holders of preregistration posts, including case conferences, teaching seminars, and meetings of a journal club."

Of all branches of education the one that leads to the practice of medicine must be unique in the volume and variety of discussion it evokes. Innumerable papers have been published on it, some of them in journals wholly devoted to the subject, of which the latest to be launched is the *British Journal of Medical Education,* the journal of the Association for the Study of Medical Education (A.S.M.E.). Three world conferences held by the World Medical Association have made a series of weighty contributions, and at present a Royal Commission is in existence to advise on future developments. Against a background of continual experiment and change the latest report from the G.M.C. may be seen as making some practical recommendations from a thoroughly contemporary viewpoint.

[1] *Recommendations as to Basic Medical Education*, 1967. General Medical Council.
[2] *Brit. med. J. Suppl.*, 1966, 1, 116.
[3] *Medical Education. Memorandum of Evidence Submitted by the British Medical Association to the Royal Commission on Medical Education, 1966.* British Medical Association.
[4] *Brit. med. J.*, 1966, 2, 125.

## Reports on Gentamicin

A recently discovered antibiotic, gentamicin, is an aminoglycoside. It is a first cousin of neomycin, kanamycin, and others,[1] and has a similar spectrum, identical pharmacological behaviour, and the same predilection for the eighth nerve, though for the vestibular rather than the auditory branch. Its most notable property is a high degree of activity against *Pseudomonas aeruginosa,* and it has been chiefly for treating infections by this organism that gentamicin has been used in the country of its origin, the United States. These have been mainly infections of the urinary tract but have included pneumonia, bacteriaemia, and burns, which responded well to a combination of local and parenteral therapy.

Hitherto the only report on gentamicin in this country has been that of M. Barber and P. M. Waterworth,[2] whose *in vitro* studies confirmed the high susceptibility of strains of *Ps. aeruginosa* recently isolated in London, and that of numerous strains of staphylococci, despite the resistance of many of them to neomycin and kanamycin. The present issue of the *B.M.J.* contains four further papers on the subject which help to define the uses and limitations of gentamicin, and raise interesting questions about dosage and the prevention of toxic effects. The report by Dr. R. L. Newman and Mr. R. J. Holt (page 539) is not the first on the treatment of infection of the central nervous system, since J. O. Klein, T. C. Eickhoff, and M. Finland[3] reported successful treatment of *Ps. aeruginosa* meningitis in an infant three years ago, but the present report concerns three cases of Gram-negative meningitis (one caused by *Ps. aeruginosa* and two by *Klebsiella aerogenes*) complicating operation for meningocele or meningomyelocele, all treated successfully. Gentamicin was given both intramuscularly in full doses and intraventricularly in daily doses of 1 mg. without ill effects. In the study reported by Dr. J. R. Curtis, Dr. S. J. McDonald, and Mr. J. H. Weston (page 537) the object of giving gentamicin to two of the patients was to control *Ps. aeruginosa* infection of a shunt-site during chronic intermittend haemodialysis, and in this it appears to have been successful. This study is mainly concerned with the long persistence of

[1] *Brit. med. J.*, 1967, 1, 158.
[2] Barber, M., and Waterworth, P. M., ibid., 1966, 1, 203.
[3] Klein, J. O., Eickhoff, T C., and Finland, M., *Amer. J. med. Sci.*, 1964, 248, 528.
[4] Jao, R. L., and Jackson, G. G., *J. Amer. med. Ass.*, 1964, 189, 817.

gentamicin in the blood of patients with end-stage kidney disease, and the authors conclude that in such patients, having dialysis twice a week, a therapeutic effect can be maintained by giving a dose of 1 mg. per kg. body weight at the end of each dialysis. It is important to recognize that from adequate data a safe and effective dose of almost any antibiotic can be calculated even for a patient with total anuria. These authors have also verified that gentamicin, like other aminoglycosides, is eliminated by renal dialysis.

The two other contributions appear to be more discouraging therapeutically. Drs. A. Pines, H. Raafat, and K. Plucinski (page 543) administered gentamicin both intramuscularly and by inhalation to 23 patients with long-standing purulent bronchitis and *Ps. aeruginosa* or *Kl. pneumoniae* in their sputum. Of 36 courses of such treatment only seven produced benefit, but this result must appear favourable by comparison with that of administering colistin by the same routes, which benefited none of 17 patients. Such unpromising clinical material, the late stage of an inevitably progressive disease with irreversible structural changes, is a hard test for any antibacterial drug. Several patients in whom the blood level of gentamicin exceeded 10 $\mu$g./ml. had dizziness and ataxia, indicating an effect on the vestibular apparatus, but these symptoms subsided when treatment was stopped. The clinical results reported by Dr. J. H. Darrell and Miss Pamela M. Waterworth (page 535) are only incidental to their argument that the dosage of gentamicin now being recommended may often be inadequate. Blood assays in normal subjects and in patients under treatment showed that concentrations adequate to deal with *Ps. aeruginosa* may be maintained for only two to three hours after a dose, the usual interval between doses being eight hours. Still more disturbing is the observation that in three patients in whom treatment failed to eliminate the organism its resistance to gentamicin increased by 8-, 8-, and 16-fold. This was accompanied in each case by an increase in resistance to all other available aminoglycosides, including streptomycin, an interesting example of one-way cross-resistance, since increased resistance to kanamycin is compatible with sensitivity to gentamicin.

The fact that gentamicin is more ototoxic as well as antibacterially more active than related antibiotics is recognized in the very modest scale of dosage at present recommended. This is a maximum of about 240 mg. daily, whereas the regular daily dose of kanamycin is 1 g., which may even be exceeded for a short time. How far can this dose of gentamicin safely be increased? The probability is that in a patient with perfect renal function it could be exceeded considerably. There is, so far as we are aware, no record of vestibular damage except in patients with known impairment of renal function, such as the five reported by R. L. Jao and G. G. Jackson,[4] or of such age that some impairment must exist even if not demonstrable by ordinary means, an example being their patient aged 69 successfully treated for pseudomonas septicaemia. It is well established that ototoxic antibiotics are more dangerous in patients over 40, and it may well be that capacity to excrete them is impaired earlier than any other function of the kidney, certainly than the capacity to excrete urea.

Further studies of the blood levels attained after different doses are evidently desirable, and another aim should be to examine carefully the relationship between vestibular impairment and dosage and duration of treatment. The fact that early changes are apparently reversible is encouraging to such study. This must mean that exploration in the field of higher dosage should be undertaken only where full facilities exist for control by blood assays. These facilities are indeed desirable, at least for the present, whenever this antibiotic is given parenterally. This further addition to the burden of the clinical laboratory is second in importance only to the tests on which the choice of a suitable antibiotic for treatment can be based.

# Consequences of Tobacco Research

Last week the Tobacco Research Council published a report on its work.[1] Its publication poses the question: Who should now do what?

When in 1954 the results of two big epidemiological studies[2 3] established beyond reasonable doubt an association between tobacco-smoking and lung cancer, the tobacco industry in Britain was unprepared to meet the new situation in which it found itself. Justly proud both of its skill in product control and of its good record in management–worker relationships, the industry in general simply could not believe that tobacco is really dangerous to health, so that the proposition was rejected with genuine emotion by employees at all levels. On the advice of the Minister of Health a hasty decision was made to donate £250,000 to the Medical Research Council, in the belief that this would be sufficient to clear up the position from a scientific point of view.

Unfortunately, the M.R.C., like the industry itself, also lacked laboratory space and suitably trained scientists to undertake relevant research, and it soon became apparent that the money given by the industry would be exhausted without any real change in the scientific position. The industry therefore set up its own laboratories at Harrogate, where the first experiments began in 1962. Gradually during the last five or six years the industry, though it does not yet accept the full hazard of smoking to health, has come to realize that if it is to continue to sell tobacco, which is its primary function, it must itself have the facilities to investigate the chemical, pharmacological, and toxic properties of tobacco smoke. The dawning of this truth has recently been accelerated by the results of the first experiments at Harrogate. These confirmed fully that smoke condensate induces skin cancer in mice and that condensate which is not more than 24 hours old is, if anything, slightly more potent than condensate stored for longer periods.

Apart from the work at Harrogate much valuable research has been generously supported by the Tobacco Research Council. This is clearly and honestly recorded in the review just published. In the event much of the work has confirmed the industry's worst rather than its best hopes. Epidemiological studies have regularly shown that smoking predisposes to chronic bronchitis, to lung cancer, to cardiovascular disease, and, when women smoke during pregnancy, to reduced birth


[1] *Review of Activities, 1963–66*, 1967. Tobacco Research Council, London.
[2] Doll, R., and Hill, A. B., *Brit. med. J.*, 1954, **1**, 1451.
[3] Hammond, E. C., and Horn, D., *J. Amer. med. Ass.*, 1954, **155**, 1316.
[4] Roe, F. J. C., and Walters, M. A., *Progr. exp. Tumor Res.*, 1965, **6**, 126.
[5] Pike, M. C., and Roe, F. J. C., in *The Prevention of Cancer*, ed. R. W. Raven and F. J. C. Roe, 1967, pp. 170–180. London.
[6] Dean, G., *Brit. med. J.*, 1966, **1**, 1506.
[7] Boucot, K. R., Cooper, D. A., Weiss, W., and Carnahan, W. J., *J. Amer. med. Ass.*, 1966, **196**, 985.