There is another cogent reason for doubting the biological significance of the experimental results presented here. Certain types of biological activity, in addition to teratogenicity[1], are commonly found in association with carcinogenicity, particularly antimitotic activity, tumour-inhibitory activity, and mutagenicity. If thalidomide possesses such activities it does so only in small degree. The suggestion that thalidomide may possess tumour-inhibitory activity[2,3] met with negative results in practice: Bach *et al.*[4] saw no inhibition of two transplantable mouse tumours, and, at the Chester Beatty Institute, we saw no inhibition of growth of the transplantable Walker rat carcinosarcoma 256 in response to thalidomide administered orally or intraperitoneally in repeated large doses. Roath *et al.*[5,6] observed "an inhibition of some aspects of cellular activity" in leucocyte cultures exposed to thalidomide, but the significance of their findings has been disputed[7]. Lüers[8] found no evidence that thalidomide causes mutations in *Drosophila*.

This investigation was supported by grants to the Chester Beatty Research Institute (Institute of Cancer Research: Royal Cancer Hospital) from the Medical Research Council, the British Empire Cancer Campaign, the Tobacco Research Council, and the National Cancer Institute of the National Institutes of Health, U.S. Public Health Service.

F. J. C. Roe
B. C. V. Mitchley

Chester Beatty Research Institute,
Institute of Cancer Research:
Royal Cancer Hospital,
Fulham Road,
London, S.W.3.

[1] Millen, J. W., *Lancet*, ii, 599 (1962).
[2] Hunter, T. A. A., *Lancet*, ii, 400 (1962).
[3] Rogerson, G., *Lancet*, i, 691 (1962).
[4] Bach, A., Bichel, J., and Hejgaard, J. J., *Lancet*, i, 1271 (1963).
[5] Roath, S., Elves, M. W., and Israëls, M. C. G., *Lancet*, ii, 813 (1962).
[6] Roath, S., Elves, M. W., and Israëls, M. C. G., *Lancet*, i, 249 (1963).
[7] Lindahl-Kiessling, K., and Böök, J. A., *Lancet*, ii, 405 (1963).
[8] Lüers, H., *Lancet*, ii, 1332 (1962).

IMMUNOLOGY

Template Requirement in the Primary Antibody Response

In most considerations of the role of the antigen in antibody formation the assumption is made that a template is either formed or activated. A template, by definition, is a system whereby many replicas are produced. The need for a template is based largely on the secondary response in which large quantities of antibodies are produced in response to small quantities of antigen over a long period of time. This, indeed, does appear to require a template. I wish to question whether the information available indicates that primary antibody formation requires a template.

In earlier papers[1-3], we have discussed quantitative aspects of the antibody response. In one of these papers[2] a graph was constructed relating antigen dosage to antibody response for diphtheria toxoid and poliovirus in man. The secondary responses showed much more antibody formed than antigen administered: 10^{-12} moles of diphtheria toxoid/kg produced about 10^{-6} moles of antitoxin/l. while 10^{-14} moles of poliovirus/kg produced about 10^{-12} moles of antibody/l. The primary responses were in marked contrast to this: 10^{-9} moles/kg of toxoid produced about 10^{-9} moles of antitoxin/l. and 10^{-14} moles/kg of poliovirus produced about 10^{-14} moles of antibody/l.

It is true that serum protein antigens do not appear to follow this pattern. For example, rabbits given a primary intravenous injection of 8×10^{-8} moles/kg of bovine-γ-globulin produced 6×10^{-6} moles/l. of antibody[4]. Similarly, chickens given 2×10^{-7} moles/kg of bovine or human-γ-globulin produced respectively 2×10^{-5} and 1×10^{-5} moles/l. of antibody while 4×10^{-7} moles/kg of bovine or human albumin produced 2×10^{-5} and 1×10^{-5} moles/l. of antibody[5]. In all these cases the amount of antibody formed is approximately two orders of magnitude greater than the amount of antigen given. It should be stressed, however, that serum proteins given as single injections are always used in considerably larger doses than are antigens of microbial origin. This raises the question as to whether a primary response is being measured or a combination of primary and secondary responses. The latter concept gains some support from the fact that a secondary response to bovine-γ-globulin is only about twice the primary response[4].

While such calculations cannot be precise, it is difficult to believe that two antigens used in very different amounts, of different origins and of different antigenicity should both produce in the order of 1 molecule of antibody for 1 molecule of antigen as a purely accidental phenomenon. If on primary immunization this is true, then a template need not be postulated. While direct use of the antigen for a single moulding of antibody is attractive, this appears inconsistent with present-day knowledge of protein synthesis mediated by RNA. The clonal selection theory sees antigen as playing a purely stimulatory part in the replication of lymphoid cells already producing the specific antibody. It is difficult to see how this would be consistent with a 1 : 1 ratio of antigen and antibody.

K. M. Stevens

Department of Medicine,
College of Medicine,
University of Kentucky,
Lexington.

[1] Stevens, K. M., *J. Immunol.*, **76**, 187 (1956).
[2] Stevens, K. M., *J. Hygiene*, **55**, 489 (1957).
[3] Stevens, K. M., and Pietryk, H. C., *Fed. Proc.*, **18**, 599 (1959).
[4] Stevens, K. M., and Riley, P. A., *J. Immunol.*, **76**, 181 (1956).
[5] Schmidt, M. H., and Wolfe, H. R., *J. Immunol.*, **71**, 214 (1953).

Active Immunization of a Human Being against Cobra (*Naja naja*) Venom

Because of the complexity of venom proteins and their great local and systemic effects, active immunization has been confined to animals utilized in the production of commercial antivenins. In work recorded here, the feasibility of a safe and practical method of immunization of man against snakebite has been explored.

Parrish and Pollard[1] found that immunity against the effect of snakebite did not exist among 14 human subjects, each of whom had been bitten twice or more by crotalid snakes. However, the development of a persistent immunity might not be anticipated in this group because envenomation occurred from 2-year to 14-year intervals, and the members of the group were also treated with antivenins following snakebite. The first observation of active immunization against snakebite was reported by Haast and Winer[2]. A subject (human) was given repeated injections of crude cobra venom over a period of 2·5 years. A maximal injection of 40 mg of venom was tolerated; this quantity of venom is lethal in the absence of immunity. Immunological tests were not performed with the serum or globulin to determine the degree of protection afforded by these injections; but the 40 mg immunizing dose of venom he tolerated is significant.

Wiener[3] described in one human subject the titre rise and persistence effected by repeated injections of Australian tiger snake venom. This subject survived the bite of a snake of this species with little difficulty subsequent to his immunization.

In this laboratory, in an attempt to measure the development of neutralizing antibodies, a human subject