membrane. Other receptors, such as those through which mitogens act, probably bind growth factors released by other lymphocytes. At what stages in ontogeny the cells respond to which stimuli is, however, still unclear, partly because of the problem of isolating cells at a defined stage. F. Melchers (Basel Institute for Immunology) was unable to shed any new light on early stages of B cell ontogeny but believes he has clarified the nature of the cell–cell signals that induce the T-cell-dependent production of antibody in B cells expressing surface immunoglobulin.

Three cell types and at least three signals are needed to induce antigen-specific, T-cell dependent immunoglobulin production by B cells. The three cells are the B cell itself, an antigen-specific T cell, and an antigen-presenting cell. The three signals are, first, the antigen; second, a surface antigen coded by the Ia region of the MHC complex and expressed on all three cells: this antigen must be recognised by the T cell as 'self' for the interactions to work (that is, they are MHC restricted); and third, a growth factor produced as a result of the interaction of antigen, T cell and antigen-presenting cell. Melchers has been able to show that the effect of the growth factor depends on the state of differentiation of the B cell. A small, 'resting' B cell that has not encountered antigen will respond with terminal differentiation to an antibody-secreting cell. After stimulation with antigen, the B cell becomes a larger, activated blast: blast cells respond to growth factor with both proliferation and antibody secretion.

One important implication of this schema is that the growth factor itself need not be antigen-specific: the antigen-specificity of the response resides in the induction of growth-factor production, and the induction of blast cell differentiation in B cells. In view of the controversy which has for some time surrounded the question of whether growth factors are, are not, or are sometimes antigen-specific, a system in which at least the cell types and their responses, if not the signals themselves, are defined, could provide important clarification.

On the other hand, this schema is only one among many and is unlikely to settle the issue definitively. Participants were quick to point out, for example, that at present this result can be obtained only with sheep red blood cells, and not with soluble antigens. The eventual clarification of such interactions may well depend on more and better definitions of subsets of cells.

Heavy chain switch

In the normal course of events *in vivo*, the activation of B cells by antigen probably also triggers the heavy chain switch. There is now mounting evidence that chromosomal rearrangements like that which brings about the V–J join also bring about the heavy-chain switch. Honjo and Kataoka[7] were the first to produce evidence, from the hybridisation kinetics of heavy chain mRNA probes with myeloma DNA, that the switch is accompanied by the deletion of the genes coding for the C regions expressed earlier in ontogeny. If deletion is the mechanism of the heavy chain switch, it follows, first, that the ordering of the C genes on the chromosomes should correspond to the order in which they are expressed in ontogeny; and second, that the switch should be irreversible. Genetic evidence from recombinant mouse strains however suggests that the δ chain gene is closer to the V genes than that of the μ chain (W.E. Paul, National Institutes of Health), which runs counter to the first prediction; and myeloma cells in culture seem to be able to switch back and forth between the three subclasses of γ chain (K. Rajewsky, Köln University), which runs counter to the second prediction.

However, the genetic evidence, while suggestive, is not conclusive, and the spontaneous reversion of the myeloma cells could be due to abnormal or unstable chromosome complements. In the meantime, evidence consistent with deletion continues to accrue from investigations on chromosomal DNA. Restriction analysis shows that J genes are near the μ gene in germline DNA[8], and that μ genes have disappeared from myelomas secreting γ_1 chains, μ and γ_1 genes from myelomas secreting γ_{2b} chains, μ, γ_1 and γ_{2b} genes from myelomas secreting γ_{2a} chains, and μ and all three γ subclass genes from cells secreting α chains[9].

Differences in membrane and secreted Igs

There is now good evidence that the last step in B cell differentiation, too, is marked by a change in the primary structure of the immunoglobulin molecule: membrane and secreted immunoglobulin are not the same. R.M.E. Parkhouse (National Institute for Medical Research, London) has used a charge-shift electrophoretic assay for detergent binding to show that the constant region fragments of membrane immunoglobulin M and immunoglobulin D have hydrophobic regions not present on the secreted molecule; and P. Vassalli (Geneva University) finds differences in the cyanogen bromide fragment patterns of membrane and secreted immunoglobulin M, though he declined to say in which part of the C region the difference lay. This is a matter of some importance because the membrane and secreted molecules seem to be identical at the C terminal[10] and the difference must therefore be internal.

This question is not likely to be resolved by analysis of the chromosomal DNA, which has so far failed to reveal more than one gene for each immunoglobulin class. At present, it is widely suspected that the switch from membrane to secreted immunoglobulin is due to differential processing of the primary RNA transcript in the nucleus. Since each of the four domains of the C region is coded by regions of DNA separated by noncoding intervening sequences, it is easy to see how differential splicing could produce changes within the C region and not only at its C terminal.

If the existence of one gene for each immunoglobulin class is confirmed, then strong support for the theory of differential splicing is provided by evidence for at least two[11] and perhaps as many as four[12] different immunoglobulin mRNAs in the cytoplasm; and B cells, which were among the first cells in which genes were discovered to contain intervening sequences, may prove to be invaluable in clarifying how the intervening sequences are removed in the course of gene expression. □

1. Le Douarin, N.M. *Cold Spring Harbor Symp. quant. Biol.* xxx, xxx (1978).
2. Burrows, P., Lejeune, M. & Kearney, J.F. *Nature* **280**, 838-840 (1979).
3. Brack, C. Hirama, M., Lenhard-Schuller, R. & Tonegawa, S. Cell **15**, 1-14 (1978).
4. Seidman, J.G. & Leder, P. *Nature* **276**, 790-795 (1978).
5. Schilling, J. Clevinger, B., Davie, J.M. & Hood, L. *Nature* (in the press).
6. Sakano, H. Huppi, K., Heinrich, G. & Tonegawa, S. *Nature* **280**, 288-294 (1979).
7. Honjo, T. & Kataoka, T. *Proc. natn. Acad. Sci. U.S.A.* **75**, 2140-2144 (1978).
8. Davis, M.M. *et al. Nature* (in the press).
9. Rabbitts, T.H., Forster, A., Dunnick, W. & Bentley, D.L. *Nature* (in the press).
10. McIlhinney, R.A.J., Richardson, N.F. & Feinstein, A. *Nature* **272**, 555-557 (1978).
11. Singer, P.A., Singer, H.E. & Williamson, A.R. *Nature* (in the press).
12. Perry, R.P. & Kelley, D.E. *Cell* **18**, 1333 (1979).

100 years ago

AFGHAN ETHNOLOGY

THE events now in progress on the north-western frontier of British India have for the third time in this century directed the serious attention of statemen, historians, and ethnologists to the remarkable people who give their name, or rather one of their names, to the north-eastern division of the Iranian table-land. During the empire of the Sassanides the whole of this region, was known as Khorasan, that is, Khoristan, the Land of the Sun or the East. This term, with the gradual reduction of the Persian sway, has shrunk to the proportions of a province on the north-eastern frontier of the Shah's estates, and has been replaced further east by the ethnical expressions Afghanistan and Balochistan, the lands of the Afghans and Baloches. . . the subjoined rough estimate of the population [of Afghanistan] according to nationalities will show that it is very far from being homogeneous:-

Afghans and Pathâns	Iranian stock	3,520,000
Tajiks	Iranian stock	1,000,000
Hindkis	Hindu stock	500,000
Hazaras and Aimaks	Mongolo-Tatar stock	600,000
Kataghâns	Tûrki stock	200,000
Badakshis	Galcha stock	100,000
Baloches	Iranian stock	100,000
Kizl-Bashes	Tûrki stock	75,000
Kohistanis and Siah Posh	Galcha stock	50,000
		6,145,000

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