群馬大学

'12

推 薦

医学部医学科小論文問題2

注 意 事 項

1. 試験開始の合図があるまで問題冊子を開いてはいけません。
2. この問題冊子のページ数は8ページです。問題冊子、答案用紙（4枚）及び下書き用紙（3枚）に落丁、乱丁、印刷不鮮明などがある場合には申し出てください。
3. 解答は指定の答案用紙に記入してください。
   (1) 文字はわかりやすく、横書きで、はっきりと記入してください。
   (2) 解答の字数に制限がある場合には、それを守ってください。
   (3) 訂正、挿入の語句は余白に記入してください。
   (4) ローマ字、数字を使用するときは、ます目にとらわれなくてもかまいません。
4. 試験時間は90分です。
5. 答案用紙は持ち帰ってはいけません。
6. 問題冊子と下書き用紙は持ち帰ってください。

次の文章を読んで，設問A～Hに答えなさい。星印（＊）のついた単語には，文末に訳注があります。

FROM MEDICINE IN AMERICA TO SCIENCE IN THE UNITED KINGDOM

After obtaining degrees in science and medicine at McGill University*, I completed a rotating internship* and a year of medical residency* at the Royal Victoria Hospital* in Montreal. I then did a three-year residency in neurology at Massachusetts General Hospital* (MGH) in Boston in preparation for a career in academic neurology* in America. Halfway through my residency, however, the Vietnam War and a change in the American draft law* prompted me to exchange my Immigrant Visa for an Exchange Visitor Visa, which meant I had to leave the United States at the end of my neurology training.

A friend at MGH, Barry Arnason, suggested that I follow in his footsteps and do immunology* before returning to neurology. After reading an article in *Science** that described some of the exciting immunology going on at the National Institute for Medical Research* (NIMR) in London, I applied to work with Avrion (Av) Mitchison there. I had not heard of either the NIMR or Mitchison and couldn't understand most of the article. Because Barry had said it would be difficult to get a place at the NIMR, I chose to write to Mitchison, whose work seemed especially impenetrable*, which I figured might put off potential applicants. It worked—but mainly because Mitchison liked the idea of having someone in his laboratory who knew something about the nervous system*. He outlined a potential research project, which I couldn't understand and never carried out. Nonetheless, I used it in my application to the American Multiple Sclerosis Society* for a postdoctoral fellowship, which was granted, even though I was a Canadian planning to work in the UK on a problem that seemed unrelated to multiple sclerosis ((A)<u>those were clearly the good old days</u>).

T AND B CELL BIOLOGY AT THE NATIONAL INSTITUTE FOR MEDICAL RESEARCH

I arrived in London in the fall of 1968. I was 30 years old and knew almost no immunology and even less about experimental science. It did not take me long, however, to appreciate that, by sheer good luck, I had landed in science heaven. (B)<u>Av was an ideal mentor*</u>, and the NIMR was a perfect environment to learn science, as it was buzzing* with outstanding scientists in many fields, especially in immunology.

(C)<u>It was an exciting time in immunology.</u> It had been known for years that lymphocytes* make adaptive* immune responses, but only in the late 1960s was it becoming clear that there are two major, functionally distinct classes of lymphocytes: T cells and B cells. Because the two cell types look the same and occur together in various lymphoid organs*, there was a pressing need for methods to distinguish and separate them in order to study their distinctive properties and functions. Av had recently heard the Boston immunologist Arnold Reif describe a protein called theta (later called Thy1) that was present in the brain and on the surface of mouse thymus* lymphocytes. As T cells develop from thymus lymphocytes, Av speculated that Thy1 might also be present on T cells but not on B cells and therefore could be a useful cell-surface marker for T cells. My task was to find

out if he was right. Av gave me Reif 's papers and set me free. The scientists with whom I shared a lab were remarkably supportive and patient and tutored me in both immunology and experimental methods. As a result, within a few months my experiments were working. To detect Thy1 on lymphocytes, I used an anti-Thy1 antiserum* prepared by Av and (D)an antibody* and complement*-dependent, ^{51}Cr-release, cytotoxicity* assay* perfected by a labmate*, Marion Ruskowicz. Making use of T cell–deficient mice generously provided by Sandra Nehlsen (a Ph.D. student of Peter Medawar, who worked across the hall), I was soon able to show that Thy1 is present on mouse T cells but not B cells, thus providing a powerful way to distinguish and separate the two types of lymphocytes.

I then used anti-Thy1 antibodies to analyze a cell-transfer system that Av had developed to study the cooperation between different populations of lymphocytes. One population comes from mice immunized* with a small hapten* coupled to a carrier protein and the other from mice immunized with a second carrier protein. When the two populations are transferred into irradiated* mice, which are then immunized with the hapten coupled to the second carrier protein, the mice produce large amounts of antihapten antibodies (Figure 1). Before transferring the cells, I treated one population or the other with anti-Thy1 antibodies and complement to kill the T cells and showed that the cooperating cells immunized with the second carrier protein are T cells, whereas the other cooperating cells, which produce the antihapten antibodies, are not. (E)This experiment provided direct evidence that T cells recognizing antigenic determinants on a protein can help B cells make antibodies against a different antigenic determinant. It also established the value of cell-type-specific antibodies that recognize cell-surface antigens, which rapidly became standard tools in immunology and, more gradually, in many other branches of biology.

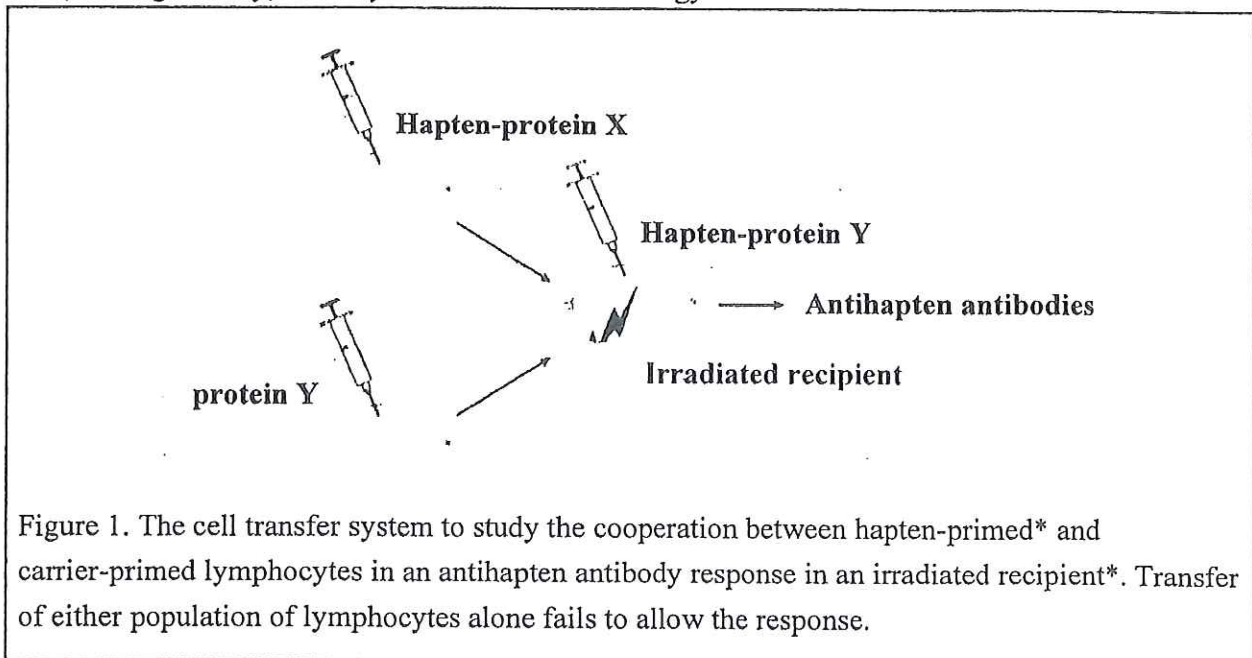

Figure 1. The cell transfer system to study the cooperation between hapten-primed* and carrier-primed lymphocytes in an antihapten antibody response in an irradiated recipient*. Transfer of either population of lymphocytes alone fails to allow the response.

Remarkably, when it came time to publish these findings, Av would not put his name on the papers even though the projects were his idea and he had begun to produce anti-Thy1 antibodies

before I arrived in London. This exceptional generosity had a transforming influence on my career. The papers gave me immediate international recognition after only two years in science, as Thy1 rapidly became a standard marker for mouse T cells. Av always did his own experiments and made many landmark contributions to immunology; because he allowed his students and postdocs* to publish on their own, however, his contributions to science are far greater than those documented in the literature.

To visualize Thy1 directly on the surface of living T cells, I turned from cytotoxicity assays to (F)immunofluorescence* experiments, (G)which quickly produced two unexpected results with important implications*. In these experiments, I visualized* the bound anti-Thy1 antibodies using fluorescent antibodies against mouse immunoglobulin* (Ig). The first surprise came from control experiments in which I omitted the anti-Thy1 antibodies, as I found that the fluorescent anti-Ig antibodies alone label a substantial proportion of spleen* lymphocytes. Roger Taylor, working across the hall, had independently obtained similar results using radioactive* anti-Ig antibodies, and we published our findings together. It was one of the first direct demonstrations of Ig molecules on the surface of lymphocytes, although many immunologists, including Av, had previously suspected that the antigen receptors on lymphocytes might be membrane-bound Ig proteins.

The finding of Ig on some spleen lymphocytes but not others raised the question of which class of lymphocyte expressed the Ig. To find out, I labeled cells with and without anti-Thy1 antibodies and examined lymphocytes from mice depleted of T cells in various ways; these experiments showed that the Ig-positive cells are Thy1-negative B cells (Figure 2). This finding led to a prolonged and frustrating search by many laboratories for the antigen receptors on T cells, which were finally identified as distinct Ig-like proteins only years later, after many false leads. Surface Ig rapidly became a standard marker for B cells in all vertebrates. （中略）

Figure 2. Immunofluorescence micrographs* of mouse spleen lymphocytes labeled with either anti-Thy1 antibodies followed by fluorescent anti-Ig antibodies (*a*) or fluorescent anti-Ig antibodies alone (*b*). By analyzing the percentages of labeled cells in each condition and by using cells from T cell–depleted mice, I could show that the cells with a cap of Ig are Thy1-negative B cells, whereas the cells with a ring of Thy1 are Ig-negative T cells.

The second surprise finding in my immunofluorescence experiments was that the Ig on the B cell surface was confined to one pole of the cell, forming a cap (see Figure 2). To determine what was special about that pole of the cell, I collaborated with Stefanello de Petris (Nello), an Italian scientist working at the NIMR. Nello was an expert in using ferritin*-coupled antibodies to localize antigens in cells by electron microscopy (EM). He labeled lymphocytes with ferritin-coupled anti-Ig antibodies at two temperatures—4℃ and room temperature. To our surprise, at 4℃ the Ig was

located in small patches* all over the B cell surface, whereas at room temperature it was all at one pole of the cell. This dramatic finding suggested that, at the higher temperature, the binding of the anti-Ig antibodies induces the membrane-bound Ig to accumulate into a cap.

(H)The next months were the most exciting and productive of my career. Nello and I returned to fluorescence experiments and quickly showed that, at 4℃, cross-linking of the surface Ig molecules by the bivalent* anti-Ig antibodies induces the Ig to cluster into patches on the B cell surface; monovalent* Fab fragments* of the anti-Ig antibodies do not exhibit this behavior unless they are cross-linked by a second layer of anti-Ig antibodies. At room temperature, the patches rapidly accumulate at the back of the cell through an active process that depends on ATP and actin* filaments (Figure 3). We found by both EM and fluorescence that antibody binding also induces endocytosis* of the surface Ig molecules; at 37℃, this clears the Ig from the cell surface, providing an explanation for the phenomenon of antibody-induced antigenic modulation previously described by Ted Boyse and Lloyd Old at the Sloan-Kettering Institute* in New York. A similar mechanism was later shown to be responsible for the downregulation of many types of cell-surface receptors* on various cell types following ligand* binding.

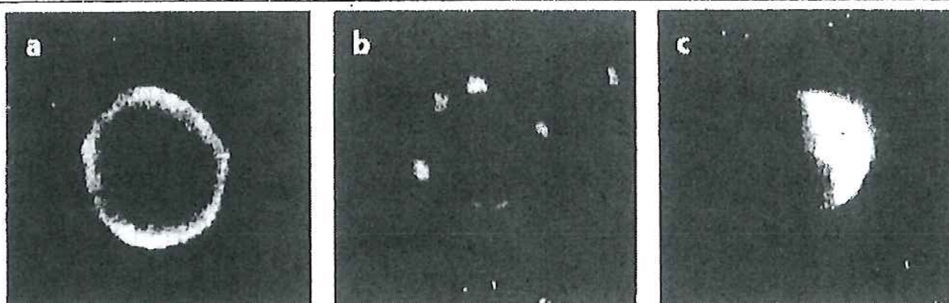

Figure 3. Immunofluorescence micrographs showing the sequence of events in antibody-induced redistribution of Ig on the surface of B cells. (*a*) The binding of fluorescent, monovalent, Fab fragments of anti-Ig antibodies at room temperature reveals a diffuse distribution of the Ig on the B cell. (*b*) The binding of fluorescent, bivalent, anti-Ig antibodies at 4℃ induces the Ig to cluster into patches. (*c*) The cells were labeled as in (*b*) but at room temperature, and the Ig patches now accumulate at the back of the cell to form a cap.

We soon discovered that our former colleague Roger Taylor, who had since moved to Bristol University*, and his postdoc Philip Duffus had similar findings. We decided to publish our fluorescence observations together in one paper before Nello and I published our EM findings, and we flipped a coin to determine the order of authors. I felt shattered when Nello and I lost the toss, as I suspected that these discoveries would be the most important of my career, which turned out to be right. The finding that cell-surface Ig molecules can move in the plane of the membrane was among the earliest evidence that cell membranes are 2D fluids rather than 2D deformable* solids, a realization that radically changed the way one thought about membrane structure and function. Moreover, ligand-induced patching, capping, and endocytosis had implications for many other

aspects of cell biology including cell movement, cell signaling, and membrane turnover*. My collaboration with Nello transformed me from an immunologist into a cell biologist, although, initially at least, I still considered myself to be a clinical neurologist rather than a scientist.
(Raff, M. Looking Back. *Annu. Rev. Cell Dev. Biol.* 2011より一部改変)

* 訳注

McGill University	マギル大学（モントリオールにある名門大学）
rotating internship	輪番制インターン（臨床医学研修）
medical residency	専門医学（病院）実習
Royal Victoria Hospital	マギル大学医学部の附属病院の一つ
Massachusetts General Hospital	ハーバード大学医学部の附属病院の一つ
neurology	神経学，神経内科学
draft law	徴兵法（制度）
immunology	免疫学
Science	サイエンス誌（アメリカの一流科学雑誌）
National Institute for Medical Research	（英国）国立医学研究所
impenetrable	不可解な
nervous system	神経系
American Multiple Sclerosis Society	アメリカ多発性硬化症協会（多発性硬化症は神経系の難病）
mentor	研究指導者
buzz	ざわつく、がやがやいう
lymphocyte	リンパ球
adaptive	適応的な，適応性のある
lymphoid organ	リンパ系器官
thymus	胸腺
antiserum	抗血清
antibody	抗体
complement	補体（抗体と協働して細胞溶解を引き起こす作用がある）
cytotoxicity	細胞毒性
assay	検査法、分析法、評価法
labmate	研究室仲間
immunize	免疫状態にする
hapten	ハプテン（それ自体では免疫反応を惹起できないが，キャリア（担体）と呼ばれるやや大きめの分子との結合体として抗原性を発現できる分子）
irradiate	放射線を照射する（大量の放射線を照射したマウスの免疫系細胞は死滅してしまう）

prime	前もって刺激する
recipient	移植を受ける動物
postdoc	ポスドク（博士課程修了の研究者）
immunofluorescence	免疫蛍光（法）
implication	暗示するもの，影響
visualize	可視化する
immunoglobulin	免疫グロブリン（抗体を構成するタンパク質，それ自体抗原性を持ち，それに結合する抗体が存在する）
spleen	脾臓
radioactive	放射能のある
micrograph	顕微鏡写真
ferritin	フェリチン（鉄タンパク質複合体）
patch	斑点
bivalent	二価の（抗原結合箇所が２箇所の）
monovalent	一価の（抗原結合箇所が１箇所の）
Fab fragments	免疫グロブリン分子の抗原結合フラグメント
actin	アクチン（細胞骨格タンパク質）
endocytosis	エンドサイトーシス（細胞膜の一部の陥入によって形成される小胞内に，細胞外に存在する物質が封入されて細胞内に取り込まれる過程）
Sloan-Kettering Institute	スローン-ケタリング研究所（ニューヨークにある，がん研究で有名な研究所）
receptor	受容体
ligand	リガンド（受容体などの高分子と結合する分子）
Bristol University	ブリストル大学（英国ブリストルにある有名大学）
deformable	変形可能な
turnover	代謝回転

設問

A. 筆者が下線部(A) those were clearly the good old daysと述べている理由を答案用紙[2－1]のA欄に日本語100字以内（句読点を含めて）で記入しなさい。

B. 筆者が下線部(B) Av was an ideal mentorと述べている理由を答案用紙[2－1]のB欄に日本語80字以内（句読点を含めて）で記入しなさい。

C. 下線部(C)は具体的にどういうことを指しているのか，答案用紙[2－1]のC欄に日本語60字以内（句読点を含めて）で記入しなさい。

D. 下線部(D) an antibody and complement-dependent, ^{51}Cr-release, cytotoxicity assayは，予め細胞に放射性同位元素の^{51}Crを取り込ませ、抗体と補体で処理し、抗体と結合するような抗原を表面に持っているような細胞のみが溶解して細胞内の^{51}Crが細胞外に出てくるようにし、細胞外の^{51}Crを定量することにより細胞表面に抗原が存在するかどうかを調べる実験手法である。この実験手法を用いて，筆者はどのようにしてThy1がマウスT細胞表面の特異的なマーカーであることを示したのか，答案用紙[2－1]のD欄に日本語180字以内（句読点を含めて）で記入しなさい。

E. 筆者が行った実験から下線部(E) に記されている結論が導かれるのはどうしてか，答案用紙[2－2]のE欄に日本語400字以内（句読点を含めて）で記入しなさい。

F. 下線部(F) immunofluorescence experimentsとは一般的にどういう実験手法か，答案用紙[2－2]のF欄に日本語40字以内（句読点を含めて）で説明しなさい。

G. 下線部(G) に述べられている筆者が予期しなかった結果２つとは何か，答案用紙[2－3]のG-1, G-2欄に各々日本語80字以内（句読点を含めて）で記入しなさい。

H. 下線部(H)のような感慨を抱くようになった，筆者の重要な発見を記載している文を２つ，答案用紙[2－3]のH-1, H-2欄に英文のまま書き出し、答案用紙[2－4]のH-3（H-1の和訳），H-4（H-2の和訳）欄に各々日本語120字以内（句読点を含めて）で和訳しなさい。