dissolve gall stones therapeutically,²⁰ provide firm encouragement for the belief that this common and important disease may be prevented.

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Students and the developing world

In the past few years we have published many articles written by students on their electives abroad. We are glad that Dr F Shann (p 474) has written complaining about these articles because it gives us a chance to clear up what seems a widespread misunderstanding. The articles are not in any way, as Dr Shann suggests, a substitute for serious, rigorous papers on medicine in developing countries. Nor are they equivalent to the educational articles that we carry on, for instance, diabetes or brain death. We have never suggested (and never would) that medicine in developing countries is a matter for students and medicine in developed countries a matter for experts.

We have the greatest respect for those who work in developing countries, and even a cursory glance at the *BMJ* of the past few years will show many serious articles written both for and by doctors practising in developing countries. For instance, in the second half of 1981 we published a series of articles on tropical infections, and in the autumn of last year

our correspondence columns hummed with letters discussing the future organisation in Britain of training in tropical medicine. Indeed, we bend over backwards to help authors from developing countries. In the past fortnight, for example, we received a handwritten paper from China, and, although the paper was clearly not suitable for the *BMJ*, we asked a referee's advice on how the authors could prepare their paper for possible publication in a western journal.

The irony of the protests about our student elective articles (and we have received many letters from readers saying how much they enjoy them) is that usually the British students are full of admiration for the work they have seen in developing countries. Many of them end their articles by saying that they are keen to return, and many do return. Sometimes, of course, they are critical of some of what they see, and they have every right to be so: a critical component is essential for a good article, and British students are just as often critical of Western medicine. A few of the articles have been written by British students who have visited the United States, and they have at times been very critical.

Dr Shann is right in some of his suppositions about why we publish these articles. With an increasing number of student readers, we are concerned to have articles in the *BMJ* written by students. Articles on student electives are one of the best ways of achieving this end. Of the many such articles we receive, we are slowly but surely raising our standards for those that are accepted. What we look for are not articles that teach us about medicine in far away countries, because we appreciate that a young student's fleeting impressions will be of little or no educational value to those working in developing countries, but rather brightly written articles that convey their flavour and also fascinate, entertain, and amuse. Students should not be discouraged by public criticism and we are keen to consider their articles—from whatever country.

Genetics of systemic lupus erythematosus

Since the discovery of the association between ankylosing spondylitis and the antigen HLA-B27 most major diseases have come under scrutiny for possible associations with HLA groups. A general conclusion of such studies is that all conditions in which autoimmune mechanisms play a prominent part show a significant association with HLA antigens, and among the connective tissue diseases examples include rheumatoid arthritis,^{1 2} scleroderma,^{3 4} some types of systemic vasculitis,⁵ Sjögren's syndrome,⁶ and systemic lupus erythematosus.

In systemic lupus erythematosus evidence for familial or genetic factor(s) in the disease had begun to accumulate independent of any HLA studies.⁷ A family history of systemic lupus erythematosus is found in about 5% of cases. Twin studies have shown up to 67% concordance for the disease in monozygotic twins—indeed, one pair of twins had been separated by adoption from an orphanage when they were aged 6 months, brought up in widely differing backgrounds, and each developed systemic lupus erythematosus within one month of each other at the age of 14. In addition, an increased frequency of autoantibodies and diminished function of the suppressor cells have been found in otherwise healthy relatives of patients with systemic lupus erythematosus.

In white patients HLA studies have most consistently shown associations with the antigens A1, B5, B7, B8, DR2, and DR3. In particular, the haplotype A1,B8,DR3 appears to confer a relative risk for systemic lupus erythematosus of between two and five times that in controls.⁸ (This is in definite contrast to the association with DR4 recently reported in drug induced lupus, which may complicate treatment with hydralazine.⁹)

One obvious problem confronting those tissue typing patients with connective tissue disease is the classification of the disease. The lupus erythematosus cell test, for example, previously used as a cornerstone in diagnosis, may give a positive result in Sjögren's syndrome, drug induced lupus, and various other lupus "variants." During the past two decades advances have been made in identifying broad subsets of disease and their association with recognisable autoantibody profiles—for example, mixed connective tissue disease and antiribonucleoprotein, Sjögren's syndrome and anti-"Ro," drug induced lupus and antihistones, and so on.¹⁰ Though this may sharpen the definition of the disease group under study, there are few clear associations between clinical subsets and HLA antigens.⁷

As well as these results indicating a connection between the HLA system and systemic lupus erythematosus, there have been many interesting reports of the association of systemic lupus erythematosus with inherited complement deficiencies.¹¹ Systemic lupus erythematosus (and lupus like syndromes) has been reported developing in people with deficiencies of the classical pathway components C1q, C1r, C2, and C4 as well as with the terminal sequence components C5-9. These inherited deficiencies are rare and in the past have not been detected in most patients with idiopathic systemic lupus erythematosus.

Several genetic loci coding for polymorphisms of several complement proteins are now known to lie within the HLA region on the sixth chromosome. They include those encoding C2, C4A and C4B, and factor B.¹² The polymorphic variation is detected by electrophoretic or isoelectric focusing techniques. Silent or null alleles of C2, C4A, or C4B may also occur. Particular alleles (including null alleles) are found in significant association with certain HLA haplotypes¹³; for example, HLA-B8 is strongly associated with a null allele of C4A.^{13 14} Thus conceivably the abnormal frequencies of HLA antigens reported in systemic lupus erythematosus may be due to the association of these antigens with null or functionally inefficient variants of C2, C4A, or C4B.

In the Hammersmith study (p 425) 29 white patients with systemic lupus erythematosus were genotyped together with their first degree relatives. Over four fifths of the patients with systemic lupus erythematosus were found to have a null allele (usually of C4A, less often of C4B, and of C2 in one case). In comparison, null alleles were found in two fifths of a group of 42 genotyped normal people, a very significantly lower frequency. A similar trend was seen when the frequency of null alleles in the patients with systemic lupus erythematosus was compared with that in their unaffected sisters. The difference was not statistically significant in that comparison, but that may have been a consequence of the relatively small numbers in the groups. Taken in conjunction with previous observations on the susceptibility to systemic lupus erythematosus of people with inherited complement deficiencies, these results are consistent with the hypothesis that most patients with idiopathic systemic lupus erythematosus have a homozygous or heterozygous deficiency (or a non-functional allele) of one of the complement proteins.

Whether the HLA-DR antigens have an independent effect

on susceptibility to systemic lupus erythematosus remains uncertain, because in the patients studied there was also a very high frequency of HLA-DR3. This issue may most easily be decided, however, by further family studies in other populations, particularly those in which DR3 is known to be of low frequency.

If the findings described in the Hammersmith study are confirmed, and complement deficiencies prove to be important susceptibility factors in most patients with systemic lupus erythematosus, many questions will need answering. Perhaps the most urgent will be those concerned with the mechanisms of the susceptible state and whether treatment with complement has a useful role in management of the individual patient.

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Expensive innovations

Expenditure on health care has risen in virtually every western country in the past 10 years; the main reason is the rapid introduction into medical practice of a wide range of expensive innovations in treatment and investigatory procedures.

A report published this week¹ by the Council for Science and Society argues that many of these "expensive medical techniques" have been adopted by the NHS with insufficient evaluation—and some have continued in use after they have become obsolete or have been shown to be ineffective. Ex-