Oct. 18, 1986

Mr. Perry Chapdelaine
The Rheumatoid Disease Foundation.
Route 4 Box 137, Franklin TN. 37064.

Dear Perry:

Early this year Dr. Paul Pybus wrote from South Africa that it seemed that macrophages are the villains in RA. In 1976, Harvey and Nimni of the University of Southern California wrote in The Lancet for July 24, that macrophages are villains in RA. Enclosed is a copy of their report.

Best:

[Signature]
In any case, it seems impossible to state positively that a child is not a carrier of the i.a.p. trait before at least the fourth month of life. At this age, the s.d. is smaller and comparison with normal values of each group allows detection of carriers (table II).

YVES NORDMANN
BERNARD GRANDCHAMP
MIREILLE GREILIE
NGUYEN PHUONG
HUBERT DE VERNEUL

MACROPHAGES AND CARTILAGE DESTRUCTION

Str.—Mononuclear phagocytes are potentially destructive cells in rheumatoid arthritis (r.a.). They are found in the invading synovial membrane adjacent to degenerating cartilage surfaces and, when stimulated in vitro, release a variety of lysosomal hydrolases, collagenase, and cytotoxic factors. We have found that synthesis of collagen by cartilage in vitro is inhibited in the presence of low concentrations of mononuclear phagocytes, whereas collagen synthesis by skin explants under similar conditions is unaffected.

Articular cartilage and abdominal skin from eight-week-old rabbits were incubated for four days in culture medium containing 10% fetal calf serum. To some cultures, we added mononuclear leucocytes purified from rabbit peripheral blood on ‘Ficoll-Hypaque’, or mononuclear phagocytes separated from lymphocytes by attachment to plastic tissue-culture surfaces. During the last twenty-four hours in culture and after removal of the leucocytes by centrifugation, the medium was supplemented with ascorbate (50 μg/ml) L-amino-propionitrile (125 μg/ml) and I-proline (50 μg/ml). Collagen synthesis was estimated by analysis of [3H]-hydroxyproline after acid hydrolysis and separation on the 50 cm column of a JEOL-SA1 aminoacid analyser. The degree of degradation of newly synthesized collagen was estimated by purification of native collagen and identification by S.D.S.-acylamide gel electrophoresis. The results were:

<table>
<thead>
<tr>
<th>Cells added to culture medium</th>
<th>Mononuclear leucocytes</th>
<th>Mononuclear phagocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue</td>
<td>(7x10⁶/ml)</td>
<td>(10⁶/ml)</td>
</tr>
<tr>
<td>Cartilage</td>
<td>1.5±7*</td>
<td>14.4±4</td>
</tr>
<tr>
<td>skin</td>
<td>104±8</td>
<td>93±11</td>
</tr>
</tbody>
</table>

*Radioactivity recovered as native collagen and expressed as percentage of control cultures x 100.

In a similar experiment, 10⁶ mononuclear phagocytes per ml reduced [3H]-hydroxyproline synthesis by cartilage to 25% of control values. The mode of action seems to be directly related to an inhibitory effect on collagen synthesis, since degradation of radioactively labelled collagen accounted for only 12% of the total decline in labelled collagen.

These results emphasise the potential role of mononuclear phagocytes in cartilage destruction in r.a., and suggest that the soft connective tissues of the joint may escape destruction as a result of their apparent insensitivity to cytotoxic factors released by mononuclear phagocytes, and to their intrinsic capacity to repair.

This work was supported by N.I.H. grants AM-10358 and AM-16404.

Department of Medicine and Biochemistry, Clinical Immunology and Rheumatic Disease Section, University of Southern California, Los Angeles, California 90033, U.S.A.

WILSON HARVEY
MARCEL E. NIMNI

VARIOCOSE VEINS IN DEVELOPING COUNTRIES

Str.—The many reports suggesting that varicose veins are rare in developing countries compared with Western countries have been based on anecdotal evidence. Although the uniformity of such reports is strong evidence of low prevalences of varicose veins in these countries, more facts are required.

Population samples were examined for varicose-vein prevalence by three of us working in very different circumstances. One of us (K.P.) examined 294 pregnant women at or near term from three different racial groups in Mombasa, Kenya. All but 1 were under the age of 41. Table I shows the percentage of varicose veins in each group. Although only a quarter of the Africans were working in some profession, 4 of the 5 with varicocese were from this group, the most severely affected being a nursing sister. The Indians, in whom the prevalence was highest, represent a higher socio-economic group who tend to be more westernised than those in India, which might explain the higher prevalence among them of varicose veins in late pregnancy than the 1.1% in pregnant women in South India.

Another of us (A.T.) examined the legs of 1000 adults (male and female) in Thailand and found mild varicocese in 63, severe enough to warrant operation in only 1.

Another (K.S.) working amongst the Triague and Mangati tribes in a rural area in Tanzania only slightly influenced by Western culture observed varicose veins in only 2 of 179 adult males (1.1%) and 3 of 163 adult women (1.8%) who were specifically examined for the presence of varicocese. These observations contrast with Coon's figure of 18.2% for all women aged 20–39 in Michigan, U.S.A. They suggest the influence of Westernisation on the prevalence of varicose veins, as indicated in a Polynesian study which showed a progressive increase following the impact of Western culture (table II). Populations in Pukapuka and Tokelau Islands in Polynesia have been very little influenced by Western customs, those on Rarotonga more so, and New Zealand Maoris to a great extent.

These findings conflict with the suggestion that man's erect posture, pregnancy, or genetic inheritance are primary factors in the etiology of varicose veins, though they may well be contributory factors. They are consistent with the hypothesis that fibre-depleted Western diets are associated with reduced size and increased viscosity of stools and that the straining necessitated to assist rectal evacuation raises intra-abdominal pressures.

5. Table I—Prevalence of Varicose Veins in Pregnant Women

<table>
<thead>
<tr>
<th>Race</th>
<th>No. examined</th>
<th>No. with varicose veins</th>
</tr>
</thead>
<tbody>
<tr>
<td>African</td>
<td>356</td>
<td>5 (1.4%)</td>
</tr>
<tr>
<td>Indian</td>
<td>72</td>
<td>7 (9.7%)</td>
</tr>
<tr>
<td>Arab</td>
<td>60</td>
<td>1 (1.7%)</td>
</tr>
</tbody>
</table>

6. Table II—Age-Standardised Prevalence-Rates (%) of Varicose Veins in South Pacific (15–64 Years)

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Zealand</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maori</td>
<td>33.4</td>
<td>30.7</td>
</tr>
<tr>
<td>White</td>
<td>19.6</td>
<td>19.9</td>
</tr>
<tr>
<td>Rarotonga</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pukapuka</td>
<td>15.6</td>
<td>19.9</td>
</tr>
<tr>
<td>Tokelau</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.0</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Bacterial Arthritis

BACTERIAL arthritis still has a considerable mortality and morbidity. Over 30% of patients may be left with residual joint damage and with some joints, like the hip, over 50% may be irreversibly damaged. Delay in making the diagnosis, which may average twelve days, and is often much longer, has serious implications for prognosis. Delay is one potentially controllable factor; increased awareness by clinicians of the possibility of infection is crucial if it is to be reduced, and this will depend on recognition of the many clinical presentations of joint infection.

The classical presentation of bacterial arthritis is as an acute, painful, hot and swollen single joint, but many infected joints present atypically and more than one joint may be involved. The onset may be insidious, with few features of inflammation to alert the clinician to an underlying infection. In the spine, sacroiliac joints, and hips, pain may be the only presenting feature. In infants and elderly people the clinical presentation is often non-specific. Even when the typically indolent infection of joint tuberculosis is excluded, only half the patients with bacterial arthritis may have fever or leucocytosis. Recognition of risk factors—systemic, local, and social—is important. Such factors act by increasing the chance of meeting an organism, increasing the risk of bacteraemia, or reducing the body’s capacity to eliminate organisms from the joint. Experimental evidence suggests that joints are usually extraordinarily well defended from bacterial invasion. Systemic disorders that affect the host’s response include diabetes mellitus, chronic renal failure, liver disease, malignancy, the arthritides, intravenous drug abuse, alcoholism, and immunosuppression. Local joint damage may be the result of earlier trauma, or surgery, or be due to arthritis including osteoarthritis. Age is also important, with newborns and elderly people being particularly vulnerable. Social factors include occupational exposure to animals with respect to brucellosis, while the risk of tuberculosis is greatly increased in certain racial groups (eg, people from the Indian subcontinent). Often these risk factors are compounded—eg, in rheumatoid arthritis the disease, treatment by immunosuppression or steroids, and joint damage caused by the arthritis all increase the chances of infection. Moreover, it may be difficult to distinguish infection from inflammatory synovitis, particularly if the patient is receiving steroid therapy.

Each risk group may have characteristic infective organisms, patterns of joint involvement, and clinical response. Haemophilus influenzae is the most frequent organism in newborns but seldom occurs outside this age group. In elderly individuals and those who are immunosuppressed, gram-negative bacteria are more common. Various unusual organisms may be encountered in intravenous drug abusers, in whom infection often occurs in the sacroiliac and sternoclavicular joints. These patterns of infection presumably reflect the complex relation between host and pathogen which is only gradually being understood. Occasionally it has been analysed in some detail—eg, complement-deficient patients are particularly susceptible to gonococcal infection. In normal people, systemic gonococcal infection is usually caused by complement-resistant strains, whereas local infection is more often associated with complement-sensitive organisms; to cause joint infection the organism that is complement resistant avoids triggering a key defence mediated by complement signals, which includes polymorphonuclear chemotaxis and phagocytosis.
The gonococcus, however, often affects young, healthy adults without an identified risk factor except sexual activity. By contrast, for most other organisms (including the most common, *Staphylococcus aureus*), there is usually a predisposing risk factor. Host factors also determine aspects of the clinical response—staphylococcal infection may be evident in one patient and occult in another. In view of this variation in response, the possibility of infection should be considered in the differential diagnosis of any unexplained monoarthritis, or if symptoms worsen in one joint in a patient with polyarthritis.

Identification of the organism is necessary for diagnosis and effective management. Once infection is suspected the joint should be aspirated, since synovial fluid gives the highest yield in isolating the organism. Risk of complications, the most worrying being introduction of infection, is minimal provided careful sterile technique is observed; even in steroid-treated patients with previous joint damage, iatrogenic infection seldom occurs. Culture of the synovial fluid may isolate the organism in 60% of cases. When synovial fluid cultures are uninformative, blood cultures may identify a further 14%, and culture of possible local sites of infection may identify others; this is especially important in gonococcal infections, partly because of the technical difficulties of isolating the organism and partly because the arthritis is triggered by non-infective immune mechanism. Bacterial products can trigger an arthritis in animals in the absence of viable organisms. Clearly there is overlap between "reactive" and infective arthritis which further complicates the clinical manifestations.

Diagnosis cannot wait the results of culture. The single most important investigation is demonstration of synovial fluid leukocytosis and bacteria on the gram stain. Interpretation of synovial fluid findings may be difficult. A leukocytosis of less than 20 000 × 10⁹/⁠¹ makes infection unlikely but does not exclude it, particularly if the gonococcus is responsible. A pronounced leukocytosis can occur in inflammatory and crystal-induced arthritides, but there may be concomitant infection. To avoid committing patients inappropriately to long-term antibiotic therapy—or treating infection with intra-articular steroids, other synovial fluid markers are needed, but no test is entirely satisfactory. Synovial fluid lactate and glucose levels are insufficiently sensitive. Counterimmunoelectrophoresis is useful in several infections, including haemophilus arthritis, and needs wider assessment. There may also be difficulties when infection is strongly suspected but its site is uncertain or access is difficult, as with the hip, spine, and sacroiliac joints; isotope bone scanning may localise the focus of infection and in the absence of inflammatory disease a false positive is unlikely.

Optimum therapy for infection includes admission to hospital, bedrest, antibiotics, and drainage. There are few guidelines to treatment based on clinical trials. One major controversy is whether the joints should be explored surgically or whether repeated aspiration and lavage is preferable. In the hip, vulnerability of the blood supply to capsular distension makes urgent surgical exploration essential. With increased diagnostic awareness and more rational therapy it should be possible to improve the prognosis.

**Oral Cholera Vaccines**

The possibility of preventing cholera with an oral vaccine has been given renewed prominence lately by the work of Clemens and his colleagues. These investigators carried out a rapid large-scale analysis of the protective efficacy of their combined whole-cell/toxin B subunit vaccine.

In a field trial conducted in Matlab, Bangladesh, 63 498 children and women received either killed *Escherichia coli* K12 cells (placebo), whole cells alone, or the combined vaccine and were subsequently monitored for presentation with clinical cholera or diarrhoea treatment centres in Matlab over five to six months. 4 and 11 cases were detected in the combined and whole-cell vaccine groups, respectively, compared with 26 cases in the placebo group, which suggests protective efficacies consistent with those found in previous volunteer studies. Although Clemens et al found no evidence of declining immunity, their initial analysis cannot be expected to indicate the long-term efficacy of the combined vaccine; this will be a key question in the continued follow-up of the study, since a rapid decline in immunity is a major drawback of the present parental killed whole-cell vaccine.