This choice was validated by the finding that the candida skin tests were positive in eight of the nine controls and converted to positive in most of the surviving children with kwashiorkor after refeeding. This recovery of function with feeding suggests that the defect is directly related to the nutritional status. Our finding of impaired lymphocyte transformation to phytohaemagglutinin, not to our knowledge previously reported in malnutrition, is consistent with these findings.

The correlation between lymphocyte transformation, delayed cutaneous hypersensitivity, and clinical grading of severity of kwashiorkor, and the improvement after refeeding, support the premise that lymphoid cell function is partly dependent on protein availability.

This defect of delayed hypersensitivity in infants with kwashiorkor may contribute to their high incidence and great severity of infection, though other factors such as non-specific immunity, exposure to infections, and socioeconomic conditions may be important. The finding of a normal lymphocyte transformation index and positive reactions to the skin antigens in a group of well-nourished but infected children indicates that in kwashiorkor the impaired lymphocyte function is related to protein deprivation rather than to the presence of infection.

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Requests for reprints should be sent to Dr. J. Katz, South African Institute for Medical Research, P.O. Box 1038, Johannesburg, South Africa.

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# PRELIMINARY COMMUNICATIONS

## Lymphocyte Response Depressive Factor in Multiple Sclerosis

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### Summary

**Normal serum contains a lymphocyte response depressive factor and this is more active against the lymphocytes of the blood from which the serum was obtained than against lymphocytes from a different normal blood. The suppressive factor is thus "tailor-made" to its own lymphocytes though cross-reactivity with other lymphocytes does occur. The significance of this is discussed. The suppressive factor has a higher titre in serum from patients with multiple sclerosis or other destructive neurological disease than in normal serum. This may be an instance of a general phenomenon in which lymphocyte sensitization is ordinarily accompanied by production of a suppressor factor able to damp down response so that this is controlled by an "accelerator-brake" mechanism. The possibilities of imbalance in the pathogenesis of disease and therapeutic manipulation of the level of suppressor substance are briefly discussed.**

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### Introduction

Whatever the aetiology of multiple sclerosis (M.S.) may ultimately turn out to be—infective or autoimmune—it is difficult to escape the conclusion that immunological processes (and delayed hypersensitivity in particular) play a part in the genesis of recurrent episodes of the disease. Since delayed hypersensitivity depends on lymphocyte sensitization and the autoaggression of these cells is believed to produce the disease, any means of damping-down the reactivity of such lymphocytes is of potential therapeutic importance. In the case of M.S. the putative antigen is a basic protein extractable from human brain (Caspary and Field, 1965, 1971a) and capable of producing experimental allergic encephalomyelitis in animals.

In multiple sclerosis (Hughes, Caspary, and Field, 1968; Knowles, Hughes, Caspary, and Field, 1968; van den Noort and Stjernholm, 1971) as well as in a whole variety of other conditions such as tuberculosis (Heilman and McFarland, 1966), hepatitis (Paronetto and Popper, 1970), secondary syphilis (Levene, Turk, Wright, and Grimble, 1969), ataxia telangiectasia (McFarlin and Oppenheim, 1969), and chronic candidiasis (Canales, Middlemas, Louro, and South, 1969) among others, serum has been shown to contain a factor which is able to damp down lymphocytic response to antigen. The present work studies the titre of this lymphocyte depressive factor in normal serum and in serum from patients with M.S. and other (destructive) neurological diseases. The isolation and characterization of the lymphocyte depressive factor might be of considerable therapeutic importance in the treatment of diseases due to "autoaggression" by these cells.

Research in human lymphocyte sensitization has hitherto been much hampered by the absence of a sensitive, reproducible, and quantitative method of estimation (Bloom, 1971), but recently we have described one such which we believe has these attributes—the macrophage electrophoretic slowing test (Field and Caspary, 1971b; Caspary and Field, 1971b)—and this has been used in the present work. Its principle is described below.

## Patients and Methods

The present work has been carried out exclusively on human serum. (*a*) Four normal subjects have been studied for the depressant effect of autologous and homologous serum—that is, from a different normal—on the interaction of lymphocytes with purified protein derivative of tuberculin (P.P.D.) and measles antigens, two to which there is almost universal lymphocyte sensitization—that is, normal serum has been studied on normal lymphocytes. (*b*) Serum from five normal subjects has been tested for lymphocyte depressive factor on the response of lymphocytes from patients with M.S. and other neurological disease when stimulated with encephalitogenic factor (E.F.), to which they are known to be sensitized (Caspary and Field, 1970). (*c*) Serum from seven cases of chronic M.S. has been tested in the same way for lymphocyte depressive factor on M.S. lymphocytes. (*d*) Serum from five patients with other neurological disease has been tested in the same way for lymphocyte depressive factor on other neurological disease lymphocytes. In addition, the effect of M.S. serum on other neurological disease lymphocytes and vice versa has been examined.

Where serum has been titrated it has been tested at dilutions of 1:60, 1:120, 1:240, and 1:480. Lymphocyte responsiveness to antigen has been assessed throughout by the cell electrophoresis method (as outlined below) which is ordinarily carried out in a balanced salt solution (medium 199).

In principle the method of electrophoretic macrophage slowing depends on the liberation, when antigen meets lymphocyte, of some factor (macrophage slowing factor, which may turn out to be identical with macrophage inhibition factor) with the property of causing normal guinea-pig peritoneal macrophages to travel more slowly in an electric field. For testing normal lymphocytes P.P.D. and measles antigen (grown in LLC $MK_2$ cells) has been used, with the culture alone without virus as control. In all tests with M.S. or other neurological disease patients encephalitogenic basic protein from human brain has been used as antigen. In all cases antigen has been used at a concentration of 33 μg/ml. The interaction between lymphocytes and antigen takes place in medium 199 at 20°C and pH 7·2. A detailed account of the method with full protocol and statistical analysis has been presented elsewhere (Caspary and Field, 1971a) but it must be stressed again that all measurements are made "blind." Briefly, lymphocytes are isolated from about 15 ml of venous blood, using carbonyl iron and methyl cellulose, while peritoneal macrophages are obtained from normal guinea-pigs 8-15 days after intraperitoneal injection of 20 ml of sterile liquid paraffin. The macrophage exudate is exposed to 100 rads of γ-irradiation to eliminate reactivity of the admixed lymphocytes. In carrying out a test $0·5 \times 10^6$ lymphocytes are mixed with $10^7$ irradiated macrophages in medium 199 and incubated for 90 minutes at 20°C. The macrophage migration time—that is, without antigen—is $t_c$. To other tubes the antigens to be tested are added and after incubation macrophage migration time is again measured ($t_e$).

When the effect of serum is to be measured concentrations of 1:60, 1:120, 1:240, and 1:480 are incorporated in the lymphocyte, antigen, and macrophage mixture and the macrophages again timed ($t_s$).

## Results

### NORMAL SUBJECTS

In Table I the actual migration times measured, using measles or P.P.D. as antigen, are set out. It will be seen that the increase in time is greatest in the absence of serum—that is, when the test is carried out in medium 199. When serum is present (1:60) in the reacting mixture the prolongation of migration time is less than when it is absent, and this difference is more pronounced with autologous serum than with that from another normal subject. Own serum thus has a more pronounced effect in inhibiting the lymphocyte-antigen interaction than has homologous serum.

TABLE I—*Normal Subjects. Macrophage Migration Time (sec) in Presence of Measles or P.P.D. with and without Serum (1:60)*

| Subject No. | Serum | Control (tc) i.e., No Antigen | Measles Antigen (te) No Serum | Measles Antigen + Serum ($t_s$) | P.P.D. Antigen (te) No Serum | P.P.D. Antigen + Serum ($t_s$) |
|---|---|---|---|---|---|---|
| 1 | — | 5·995* | 6·735 | | 7·055 | |
| | 1† | | | 6·595 | | 6·855 |
| | 2 | | | 6·705 | | 7·015 |
| 2 | — | 5·995 | 6·700 | | 7·100 | |
| | 2† | | | 6·620 | | 6·870 |
| | 1 | | | 6·655 | | 7·020 |
| 3 | — | 6·025 | 6·700 | | 7·080 | |
| | 3† | | | 6·610 | | 6·860 |
| | 4 | | | 6·680 | | 6·975 |
| 4 | — | 6·015 | 6·755 | | 7·020 | |
| | 4† | | | 6·635 | | 6·840 |
| | 3 | | | 6·665 | | 6·950 |

*Each time is calculated as the mean of 20 readings and the S.D. is less than 0·02 sec (full details are given in Caspary and Field, 1971a).
†Autologous serum.

The inhibition of lymphocyte response resulting from the incorporation of serum into the test system can be most conveniently expressed by representing the response in medium 199 as 100 and calculating the other results as a proportionate figure. For example in line 1 of Table I, measles antigen causes 6·735-5·995 = 0·740 sec slowing. This is taken as 100. Then in line 2, when autologous serum is present, the slowing is 6·595-5·995 = 0·600 sec and this is represented as 81·1 in line one of Table II. Table II shows the data of Table I presented in this form. Statistical calculation shows that only differences >15·0 are significant (P<0·01). The figures in Tables III-V also represent the calculated values based on 100 as representing the response in absence of serum—that is, in medium 199.

TABLE II—*Data of Table I Presented as Described in the Text: 100 Represents Migration Inhibition Result when Test Carried Out in Medium 199*

| Subject No. | Serum | Measles | P.P.D. |
|---|---|---|---|
| 1 .. .. | 1 | 81·1 | 81·1 |
| | 2 | 96·0 | 96·2 |
| 2 .. .. | 2 | 88·7 | 79·2 |
| | 1 | 93·6 | 92·8 |
| 3 .. .. | 3 | 86·7 | 79·1 |
| | 4 | 97·0 | 90·0 |
| 4 .. .. | 4 | 83·8 | 82·1 |
| | 3 | 87·8 | 93·0 |

Only a change >15·0 is significant (P<0·01).

### M.S. PATIENTS

The cells of M.S. patients tested with E.F. antigen showed well-marked sensitization to E.F. as reported previously (Caspary and Field, 1970).

(*a*) The serum of seven M.S. patients (Cases 5-11) was tested for suppressive activity in each case against own lymphocytes and this was compared with the action of homologous serum—that is from a different M.S. patient. As can be seen from Table III, an M.S. serum is much more active against own lymphocytes than is the serum from another patient on those lymphocytes. When P.P.D. is used as the provocate antigen own serum is again more effective than homologous serum—that is, from another case of M.S.

(*b*) When the lymphocyte-depressing activity of homologous M.S. serum—that is, from other cases of M.S.—was titrated on the cells of three patients (Cases 12, 13, and 14, Table IVa) it can be seen that four of the six homologous sera were active at 1:240. In Case 14 the patient's own serum (autologous) was also titrated out and found to be active to 1:480. Thus M.S. serum was more active on its own cells than were foreign M.S. sera.

TABLE III—*M.S. lymphocytes: Suppression Produced by Own Serum (1:60) Compared with that Produced by Sera from Other M.S. Patients (1:60). 100 Represents Migration Inhibition Result when Test Carried Out in Medium 199*

| Case No. | Anti-gen | Own | Homologous Serum | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 5 | 6 | 7 | 8 | 9 | 16 |
| 5 .. | E.F. | 58·3 | — | — | — | — | — | — |
| | P.P.D. | 61·5 | — | — | — | — | — | — |
| 6 .. | E.F. | 68·3 | — | — | — | 83·6 | — | — |
| | P.P.D. | 72·2 | — | — | — | 90·1 | — | — |
| 7 .. | E.F. | 36·7 | — | 63·3 | — | 52·5 | 67·1 | — |
| | P.P.D. | 56·1 | — | 72·4 | — | 64·5 | 69·6 | — |
| 8 .. | E.F. | 32·9 | — | 60·3 | 54·8 | — | 68·5 | — |
| | P.P.D. | 58·6 | — | 77·7 | 71·2 | — | 75·3 | — |
| 9 .. | E.F. | 32·4 | — | 64·2 | 83·8 | 69·6 | — | — |
| | P.P.D. | 61·0 | — | 80·3 | 81·7 | 86·7 | — | — |
| 10 .. | E.F. | 49·2 | — | — | — | 68·3 | — | — |
| | P.P.D. | 49·6 | — | — | — | 65·2 | — | — |
| 11 .. | E.F. | 40·8 | 74·6 | — | — | — | — | 52·7 |
| | P.P.D. | 61·7 | 80·2 | — | — | — | — | 65·2 |

Cases 5-11 inclusive and Case 16 suffered from M.S. Case 10 was in an acute phase. Case 11 was subacute.

(*c*) Sera from cases of other neurological disease were titrated out on lymphocytes from M.S. Cases 17 and 18. It can be seen (Table IVb) that depressant activity was preserved to 1:240. Thus other neurological disease serum has the same power to block E.F.-M.S. lymphocyte interaction as has M.S. serum itself.

(*d*) For comparison the blocking ability of normal serum (Cases 1 and 19-22) on E.F.-M.S. lymphocyte interaction was titrated. It is apparent that the activity of normal serum does not extend beyond 1:60.

It is of interest that though Cases 10 and 13 were in an acute phase of M.S. (Tables III and IV) their sera did not show greater blocking activity than those from the other patients who were chronically affected.

### OTHER NEUROLOGICAL DISEASES

Lymphocytes from patients with destructive neurological disease other than M.S. were sensitized to E.F. in much the same degree as in M.S. (Caspary and Field, 1970). Again serum from such cases depressed the response when introduced into the test system and was active in higher dilution than was normal serum. Just as serum from M.S. patients was active against other neurological disease lymphocytes (Table Vb), serum from other neurological disease patients was active in reducing M.S. lymphocyte reactivity in about equal measure (Table IVb). Similarly the serum of Case 25 (Table Va) was more active against his own cells than was homologous serum.

TABLE IV—*M.S. Lymphocyte Suppression*

| Case No. | Serum | 1:60 | 1:120 | 1:240 | 1:480 |
|---|---|---|---|---|---|
| (*a*) *M.S. lymphocytes; M.S. serum from different patients: E.F. antigen. Inhibitory factor titrated out* | | | | | |
| 12.. | 7 | 53·4 | 55·6 | 97·2 | 97·2 |
| | 8 | 57·9 | 61·2 | 66·9 | 98·9 |
| | 9 | 58·9 | 59·6 | 80·3 | 99·4 |
| 13.. | 15 | 57·4 | 66·7 | 100·6 | 100·6 |
| | 16 | 58·0 | 59·3 | 73·5 | 101·9 |
| 14.. | 13 | 59·8 | 63·4 | 77·8 | 96·9 |
| | 14 | 46·4 | 49·0 | 58·8 | 79·4 |
| (*b*) *M.S. lymphocytes; Other Neurological Diseases serum; E.F. antigen* | | | | | |
| 14.. | 17 | 58·2 | 62·4 | 77·3 | 97·4 |
| | 18 | 62·9 | 61·2 | 67·5 | 96·9 |
| (*c*) *M.S. lymphocytes: normal serum: E.F. antigen* | | | | | |
| 12.. | 19 | 84·3 | 98·3 | — | — |
| | 20 | 86·0 | 97·2 | — | — |
| 13.. | 1 | 80·9 | 92·6 | — | — |
| | 21 | 85·8 | 98·1 | — | — |
| | 22 | 87·0 | 98·1 | — | — |

Cases 5-16 inclusive suffered from M.S. (Cases 10 and 13 were in an acute phase; Case 11 was subacute). Cases 17 and 18 suffered from other neurological diseases Cases 19-22 and Case 1 were healthy normals.
Anything below 85 is $P<0{\cdot}01$.

TABLE V—*Other Neurological Disease Suppression*

| Case No. | Serum | 1:60 | 1:120 | 1:240 | 1:480 |
|---|---|---|---|---|---|
| (*a*) *Other Neurological Disease lymphocytes; serum from other patients with Other Neurological Disease; E.F. antigen. Inhibitory factor titrated out* | | | | | |
| 23.. | 28 | 69·5 | 66·5 | 76·8 | 104·9 |
| | 29 | 61·0 | 67·1 | 91·5 | 99·4 |
| | 30 | 50·9 | 53·3 | 65·5 | 95·2 |
| 24.. | 31 | 57·0 | 59·4 | 78·8 | 100·0 |
| | 18 | 57·0 | 54·5 | 67·3 | 98·8 |
| 25.. | 23 | 62·2 | 72·4 | 80·5 | 96·2 |
| | 25 | 45·9 | 57·8 | 68·6 | 82·2 |
| (*b*) *Other Neurological Disease lymphocytes: M.S. serum: E.F. antigen* | | | | | |
| 25.. | 11 | 65·4 | 65·4 | 81·1 | 96·8 |
| | 15 | 65·4 | 68·1 | 87·6 | 101·1 |
| 26.. | 10 | — | — | 56·8 | 100·5 |
| (*c*) *Other Neurological Disease lymphocytes: normal serum: E.F. antigen* | | | | | |
| 27.. | 32 | 82·4 | 98·8 | — | — |

Cases 23-31 suffered from other neurological diseases. Cases 10, 11, and 15 suffered from M.S. Case 32 was normal.

Normal serum (only one specimen tested—Case 32) (Table Vc) had much the same depressant effect on other neurological disease lymphocytes as on M.S. cells—in both cases distinctly less than the disease sera.

## Discussion

Our results indicate that there is present in the serum of normal subjects and to a greater extent in the serum of patients with destructive neurological disease (including M.S.) a factor which can exert a depressive effect on lymphocyte response to specific antigen as measured by the macrophage slowing technique. Moreover, in the case of normal serum this factor has a greater effect on its own lymphocytes than on those from other normal people. It would thus seem to be "tailor-made" to its own lymphocytes, an example of the "uniqueness of the individual." In patients with M.S. or other neurological disease, serum likewise has a greater effect on autologous lymphocytes than on those from another patient. However, there is no specificity, in that M.S. serum will depress other neurological disease lymphocytes, and other neurological disease serum will depress M.S. lymphocytes. The titre of suppressive activity is clearly greater in sera from patients with M.S. and other neurological disease than in normal serum. We have no evidence that the factor is qualitatively different.

Our finding of lymphocyte responsiveness depressor factor in serum may offer an explanation of a difficulty, not often brought out, which confronts those who attribute to M.S. an essentially autoimmune pathogenesis. It is now clear that sensitization to E.F. occurs as a consequence of brain destruction from any cause and involves both humoral and cellular aspects (Caspary and Field, 1970; Field, Caspary, and Ball, 1963), and indeed appreciable sensitization occurs in a considerable proportion of normal subjects (Field *et al.*, 1963; Caspary and Field, 1970). Why then does M.S. not follow much more frequently as a continuing autoimmune process as a sequel, say, to head injury? Though a number of suggestions might be offered, it seems possible that suppressive factor is produced under such conditions and the development of M.S. might result only from initial or periodic failure of suppressive factor to reach an adequate level. Quantitative serial study of suppressive factor titre over the period of an exacerbation would be important.

We have also established that in other conditions in which lymphocyte sensitization to a variety of antigens has been found —for example sarcoidosis, B.C.G. "non-converters" (Caspary and Field, 1971b)—a serum factor capable of depressing lymphocyte response is also to be found. Indeed the occurrence of such a factor in sarcoidosis, where high lymphocyte sensitization is so commonly accompanied by diminished delayed hypersensitivity skin reactions, is a theoretical necessity. We have found, too, that the newborn child with high lymphocyte

sensitivity to P.P.D. (Field and Caspary, 1971a) yet negative Mantoux reaction also has a high level of serum depressive factor.

The inhibitory factor is not specific, in so far as M.S. or sarcoid serum will also interfere with unrelated antigen-lymphocyte interaction. For example, serum (1:60) from a patient with other neurological disease and two M.S. sera reduced a mixed lymphocyte reaction by 23·1, 28·6, and 41·5% respectively. Likewise M.S. serum (1:60) reduced the interaction between bovine serum albumin and lymphocytes in a case of erythema nodosum by 54·8% and for egg albumen by 48·1%. A full account of these studies will be given elsewhere, but it is already clear that the development of lymphocyte sensitization (as indicated by the capacity to interact with a particular antigen) seems to be associated with the appearance in the serum of a depressant factor and that this factor is more effective against its own lymphocytes than those from another individual. In view of the many reports of depressive factor referred to in the introduction, it may be that the present study of M.S. and other neurological disease is but a special instance of a general phenomenon—the simultaneous development of lymphocyte responsiveness and a serum-mediated "damping mechanism." If further studies support this view, then we have another example of a biological "brake-accelerator" mechanism, operating this time in immunological reactivity. The suppressor element might indeed be the "feedback factor" postulated in several modern schemata involving lymphocyte activity—for example, that of Mackler (1971).

It is legitimate to speculate that disease may result from imbalance between lymphocyte reactivity on the one hand and suppressive activity of serum on the other, so that it would be reasonable to attempt therapeutic control of lymphocyte activity (either in positive or negative direction) by increasing or reducing the suppressive factor. Thus autoimmune diseases (if they exist) presumably result from a runaway activity of lymphocytes and might be treated by augmenting the level of suppressor factor. On the other hand, where lymphocyte activity is being held in check physiologically and where its greater exercise might be beneficial—for example, in resistence to cancer—it might be possible to eliminate or reduce suppressor activity. As a first step it is necessary to isolate and characterize the suppressor factor. Its relation to the factor isolated by Cooperband, Bondevik, Schmid, and Mannick (1968) is being explored, but it is already clear that it occurs in the same α2-globulin fraction in normal, M.S., and cancer serum.

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# MEDICAL MEMORANDA

## Muscle Fibrosis and Contractures in a Pethidine Addict

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Myopathy complicating intramuscular administration of some drugs is well recognized. The repeated intramuscular injection of chloroquine, for example, induces intense necrosis and phagocytosis at the injection site (Aguayo and Hudgson, 1970). Pethidine is usually injected intramuscularly, and it is perhaps surprising that there has been only one report of myopathy developing in those addicted to it (Aberfeld *et al.*, 1968). We believe that the case described here was of this kind.

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### Case Report

The patient was a 60-year-old Indian who had emigrated to England in 1968. When first seen in December 1968 he complained that for 18 months he had experienced increasing difficulty in flexing his elbows fully and for eight months a similar difficulty with his knees. He had had a cholecystectomy in 1954 and a calculus removed from the common bile duct in 1963. He was given pethidine first in 1961 for biliary colic and he continued to inject the drug with increasing frequency until the second laparotomy in 1963. After that he remained in hospital for three months, receiving pethidine 100 mg every two or three days. On leaving hospital he had continued to inject himself in steadily increasing doses up to 1,000 mg daily. At first he injected the drug only into the triceps muscles, but in 1967 he developed an abscess in the left triceps and began to inject the drug into the fronts of both thighs. When they became "woody" he used the medial aspect of the thighs and the buttocks. He did not sterilize the needles, which were about 3·7 cm long, and changed them only every two or three weeks. Since coming to England he had been persuaded by his son to stop the drug, and apart from a feeling of restlessness and insomnia he had suffered no untoward effects.