dilation of the large venules, collecting venules and veins. There was accumulation of PAS staining positive material, consistent with platelet aggregation marginated on the endothelium of small veins. Coronary arterioles showed some oedema of the intima and media with the presence of microvacuoles. There was a marked mast cell infiltration into perivascular areas of the coronary microcirculation.

In view of the results described it was necessary (i) to confirm that the microvacuoles contained lipid, (ii) to examine the ultrastructure of the endothelial lining for evidence of junctional gaps, and (iii) to search for indications of platelet aggregation within the microcirculation. Evidence is presented confirming each of the suppositions enumerated.

A time course study designed to demonstrate the onset of ultrastructural changes indicates that junctional gaps appear after 40 days of stress. Examination of plasma 11-OHCS levels indicates that the extreme elevation is maintained for at least 25 days, and thereafter declines to some 45 μg/100 ml plasma by day forty. This level of 11-OHCS is maintained through to termination of the experiment at day seventy. It is possible that a causal relationship exists between the microcirculatory changes and the reduction in circulating 11-OHCS levels.

References

BASSETT, J.R., CAIRNCROSS, K.D. & KING, M.G. (1973). Parameters of novelty, shock predictability and response contingency in corticosterone release in the rat. *Physiol. Behav.*, **10**, 901–907.

CAIRNCROSS, K.D. & BASSETT, J.R. (1975). Changes in myocardial function as a consequence of prolonged emotional stress. *Prog. Brain Res.*, **42**, 313–318.

The effect of some anti-inflammatory and anti-malarial drugs on the migration of horse leucocytes *in vitro*

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When leucocytes are packed into a capillary tube, by centrifugation, and the cell-supernatant interface is cut, they migrate fanwise from the cut end. The process has been studied extensively in relation to delayed hypersensitivity, and recently as affected by some anti-inflammatory drugs (Meacock & Kitchen, 1976). We also have examined the effects of some anti-inflammatory drugs, particularly those which also have anti-malarial activity. Migration has been inhibited by a number of such drugs, and also by chemically related compounds not known to be anti-malarial or anti-inflammatory.

Leucocytes have been obtained by allowing erythrocytes to sediment spontaneously from horse blood, yielding a leucocyte-rich plasma, which is centrifuged at 180 *g* for 10 minutes. The leucocytes are resuspended in medium 199 and are allowed to migrate for 18 h as described by George & Vaughan (1962), with minor modifications, in the presence of drug. The leucocytes comprise 80.0% (s.e. mean $= \pm 1.8$, $n = 14$) polymorphonuclear neutrophils. Migration is measured as the distance from the cut end of the capillary to the boundary of the migrating cells. Conventionally, in experiments of this type the response is measured as the area covered by the migrating cells. However, we have found that the variance of such measurements was strongly correlated with the mean ($r = +0.53$, $n = 20$, $P = 0.01$) whereas the same parameters of the distance migrated was only slightly correlated ($r = 0.21$, $n = 20$, $P = 0.34$). Potency of compounds has therefore been estimated as the concentration of drug reducing the distance of migration to 50% of the control.

The following anti-malarial drugs were tested by this method: mepacrine, chloroquine, hydroxychloroquine, chloroguanide, cycloguanil, primaquine and quinine. Drugs of similar chemical structure such as imipramine and chlorpromazine, together with aspirin, indomethacin, phenyl butazone and hydrocortisone were also examined.

We have found that mepacrine, imipramine, chlorpromazine and proguanil all inhibited leucocyte migration with EC_{50} of between 90 and 250 μM. Chloroquine, hydroxychloroquine and quinine were about 8 times less active than mepacrine and primaquine 5 times less so. Cycloguanil and conventional anti-inflammatory drugs were inactive up to 1000 μM.

These findings confirm that conventional anti-inflammatory drugs do not inhibit random migration of polymorphonuclear neutrophils. Mepacrine and chloroquine, which have been used to control rheumatoid arthritis, are active at concentrations comparable to those achieved therapeutically. It appears that inhibition of migration is neither specific to anti-malarial activity nor to chemical structure, but this activity may contribute to the anti-inflammatory activity of these drugs.

References

GEORGE, M. & VAUGHAN, J.H. (1962). *In vitro* cell migration as a model for delayed hypersensitivity. *Proc. Soc. exp. Biol. Med.* **111**, 514–521.

MEACOCK, S.C.R. & KITCHEN, E.A. (1976). Some effects of non-steroidal anti-inflammatory drugs on leucocyte migration. *Agents & Actions*, **6**, 320–325.