hypotheses, to studies on individual people, which have provided evidence for the programming hypothesis in relation to several important physiological and biochemical variables.

Secondly, there are features in the Barker group's results that argue against the most important criticism (the failure to recognise continuing adverse circumstances as a confounding factor). Barker's group have established that relations between early experience and later disease or physiological change are very specific in their times of operation. Even in the geographical studies it is not a question of all indicators of early disadvantage correlating with all the diseases of interest. Stroke is linked to earlier maternal and neonatal mortality, chronic bronchitis to postneonatal mortality, and ischaemic heart disease to both neonatal and postneonatal mortality.

If the early mortality indices were simply acting as markers of later adversity we would not expect these specific relations. Similarly, the studies on individual people show very specific relations between growth at a particular phase—for example, in fetal life or infancy—and later measurements of blood pressure, glucose tolerance, and concentrations of cholesterol and fibrinogen.

Though studies of mortality could not control for the effects of continuing socioeconomic factors because the information was not available, in the studies of living people the relations found between early weight and later risk factors were independent of socioeconomic status, either currently or at birth.^{8 9 21}

What should the uncommitted reader make of this controversy? The topic is too important to be regarded simply as an intriguing debate between two schools of epidemiology. One view would be that the Barker group are misled, either in their findings or, as Elford *et al* suggest, in their interpretation. This is difficult to accept, given the coherence and logic of the Barker group's studies, which have used several populations and sought several different types of data to test their hypothesis. Another view is that both groups are right, that both very early influences and later ones contribute to the causes of ischaemic heart disease and that the dispute is really about the relative importance of each.

Such a compromise view, however, would not explain the

geographical paradox, which began the Barker group on their inquiries. Nor do Elford and colleagues offer an alternative explanation of this in their criticisms of the programming hypothesis.

A third possibility is that we are witnessing the beginning of one of Thomas Kuhn's "paradigm shifts."²² The lifestyle paradigm for the aetiology of ischaemic heart disease seems to be unable to account for the geographical epidemiology of the disease—at least in Britain. The "early life experience" paradigm is a strong candidate for its replacement.

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The supraregional assay service

About to lose the benefits of centralisation

Few doctors have much to do with the supraregional assay service: a busy general hospital with an active clinical endocrinology department might send it requests for one adrenocorticotrophic hormone, two parathyroid hormone, and eight growth hormone assays a month. Yet the service has been a success since it was set up in 1974—a model of rationalisation. In some ways it could be taken as a microcosm of the wider NHS of which it is a part, in which case what's happening to it now as a result of the government's reforms may provide a pointer to what to expect in other parts of the NHS.

The service was set up in response to the uneven distribution of facilities providing specialised laboratory investigations.¹⁻³ More than 20 centres now provide technically complex or infrequently requested assays of hormones, proteins, tumour markers, drugs, trace metals, and enzymes in genetic tissue.

Centralisation brought its advantages. It minimised the

problems of maintaining the quality of assays done in small numbers or infrequently. (Paradoxically, results were usually available more quickly if the assays had been done locally.) The service provided hospitals with expert advice on the interpretation of results. The centres developed new assays—for example, of gastrointestinal hormones, androstenedione, and insulin C peptide. Assays previously available only from the service were improved, meaning that assays for thyroid hormones, thyroid stimulating hormone, gonadotrophins, and prolactin could be devolved to general hospitals—whose laboratory staff were offered training at supraregional centres. Because clinical chemists in referring to hospitals were responsible for ensuring that requests were appropriate, the service was less abused by inappropriate requests than many other investigative services.

Although initial funding came from the Department of Health and Social Security,⁴ local health authorities were

financially responsible for the centres' day to day running. No money changed hands between the providers and the users of the service.

This arrangement could not survive the NHS reforms. A working party with representatives from the regions, royal colleges, and the service recommended the formation of a board to represent their interests as purchasers and providers. This board came into operation last April: members included a regional general manager, a regional director of finance, a regional scientific officer, nominees from the Royal College of Pathologists and the clinical royal colleges, and two directors of the supraregional assay service. Its functions were to define the range and quality of assays, to recognise laboratories, and to decide pricing policies. An agency with responsibility for the contracts was also set up. Regions were to negotiate block contracts with individual laboratories in the supraregional assay service; payment would be by subscription.⁵

At the time this seemed a reasonable arrangement. Including senior managers on the board, it was thought, might help to identify any deficiencies of the system and to exert pressure for their solution. The new arrangement was meant to be reviewed after two or three years, but within a few months of operation patience gave way to political expediency. By last July regional general managers were asking for a different funding mechanism to start from this April. They wanted contracts negotiated between individual units and individual laboratories in the supraregional assay service, which would bypass the board. The managers have had their way.

This latest proposal is likely to have two main consequences. Firstly, hospital laboratories will be under pressure to shop around for the cheapest assay or to set up their own assays, which will counter all the advantages of centralisation. Secondly, paperwork out of proportion to the number of tests and their costs will swamp the providers and purchasers of services.

Despite its informal organisation the supraregional assay service has provided high quality assays, training, research, and, most importantly, reliable information for the clinical management of patients throughout the country. It has also been cheap to run, costing between £4m and £5m a year.⁶

One of the initial aims of the NHS when it started, and indeed one of the stated aims of the latest reforms, was that specialist services should be available to all. This principle is now under threat. Those in the macrocosm take note.

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Detecting susceptibility to malignant hyperthermia

New genetic tests and better communication among affected families could help

The safety of modern anaesthesia gives prominence to its comparatively rare complications, which include malignant hyperthermia. This condition is triggered by many commonly used inhalational anaesthetic vapours (including halothane, enflurane, and isoflurane) and perhaps the muscle relaxant, suxamethonium. It greatly increases the metabolic rate and may lead to severely deranged muscle function, muscle spasm, and rigidity. Homeostasis fails, and hypoxia, acidosis, and hyperkalaemia ensue. Unless corrected early by withdrawal of the precipitating agent and administration of dantrolene, death is likely.

Susceptibility to malignant hyperthermia is dominantly inherited with a likely candidate gene residing on the long arm of chromosome 19.^{1,2} Although the gene has not been positively identified, evidence is accumulating for an abnormality in the gene that codes for the ryanodine receptor, which controls one of the calcium ionic channels in the sarcoplasmic reticulum. This is intellectually attractive as loss of control of intracellular ionic calcium occurs during a malignant hyperthermia "crisis."³

The need for a screening test for patients who have had aborted episodes of malignant hyperthermia and for other family members who may be susceptible is self evident. Twenty years ago in vitro muscle contracture tests were developed,^{4,5} and these have become the internationally recognised standard for detecting susceptibility to malignant hyperthermia.^{6,7} Screening laboratories have been set up in most medically advanced countries, and all use this test, which requires a muscle biopsy. Phenotyping for susceptibility relies on the response of muscle to halothane and

to caffeine. Attempts at phenotyping by using other markers (such as the serum creatine kinase concentration) have been either unsuccessful or unreliable.

Malignant hyperthermia is not the only drug induced cause of a high body temperature due to metabolic stimulation. Neuroleptic malignant syndrome as described by Renwick *et al* (p 831)⁸ shares many features with malignant hyperthermia, although the in vitro muscle contracture test clearly differentiates them.⁹ Another potentially fatal syndrome, presenting with metabolic stimulation and muscle necrosis, occurs after poisoning with 3,4-methylenedioxymetamphetamine ("ecstasy").¹⁰ Whether results of in vitro muscle contracture tests are abnormal in this condition is unknown.

An important development in distinguishing these various syndromes from malignant hyperthermia would be a blood test using DNA extracted from white cells, as recently described by Healy *et al.*¹¹ Using polymorphic DNA markers that are known to locate in the region of the gene for the ryanodine receptor, the authors reported that flanking markers D19 S9 and D19 S16 generated a lod score of >3 in one large Irish pedigree. From this result they concluded that these markers could be used to diagnose susceptibility to malignant hyperthermia "in large known malignant hyperthermia pedigrees." Extrapolating their results to smaller and less intensively screened pedigrees should be avoided: they studied a single family in which no recombinants were identified—making it impossible to assess how much heterogeneity is present in people with malignant hyperthermia.

Heterogeneity (that is, more than one gene being respon-