Part 10

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3005

Confidential filing

Maintaining the Strength of the Science Base

Science Budget

[In attached folder: ACOST Report on developments in Biotechnology] Recent Stat Trend UK Science Base:

SCIENCE AND TECHNOLOGY

Part 1: Sept 1983

Part 10: Jan 1990

Referred to	Date	Referred to	Date	Referred to	Date	Referred to	Date
~~17.1.90~~							
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PART 10 ends:-

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PART 11 begins:-

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TO BE RETAINED AS TOP ENCLOSURE

Cabinet / Cabinet Committee Documents

Reference	Date
AST(90) 8	05/03/1990
AST(90) 2ND MEETING	14/03/1990

The documents listed above, which were enclosed on this file, have been removed and destroyed. Such documents are the responsibility of the Cabinet Office. When released they are available in the appropriate **CAB** (CABINET OFFICE) CLASSES

Signed _____ Date 28/11/2016

PREM Records Team

W0429

MR GRAY

March 30, 1990

PUBLIC REPORT TO ACOST

Lord Flowers wrote to the Prime Minister on 6 March suggesting that ACOST should produce a report to Parliament every other year which examined the strategic issues in science.

2. I have consulted Lord Tombs and Sir Robin Nicholson (who will become the Chairman of ACOST in July). We believe that there is merit in the idea of a periodic report from ACOST which reviews the issues in science and technology and which looks forward to those to which ACOST will need to give priority in its work. The Annual Review of Research and Development would provide a foundation for any analysis and comment. Departments are content if care is taken to avoid public lobbying for extra money.

3. It would be wrong to address this report to Parliament; rather it should be published, with the Prime Minister's approval, as other ACOST reports and made available from HMSO.

4. Lord Tombs suggested a report to be published at the end of the first year of a Chairman's term which is for three years. This would allow ACOST, early in the term of an incoming Chairman, to assess its priorities and establish a view of the issues it wishes to tackle.

5. The present terms of reference of ACOST provide for the publication of such a report and nothing additional is necessary to provide for it.

6. I attach a draft reply to Lord Flowers.

SIR JOHN FAIRCLOUGH
Chief Scientific Adviser

DRAFT LETTER TO LORD FLOWERS FROM THE PRIME MINISTER

Thank you for your letter commenting on the Government's reply to your Committee's report on Civil Research and Development and your suggestion that ACOST produce a report to Parliament every other year.

I have considered your suggestion and think there is merit in ACOST periodically preparing a strategic review of public and private sector scienceand technology which identifies the future issues which they will examine. The Chairman of ACOST is appointed for three years and it would be appropriate for ACOST, early in the time of an incoming Chairman, to prepare such a report for my approval, to be published in the same way as other ACOST reports. Such an arrangement would result in the preparation of a report every three years rather than two as you suggest.

Because ACOST is responsible to the Government, a report to Parliament would be inappropriate. A report to the Government, of course, would be as widely available as many ACOST documents. responsible to theT will discuss will be of wide interest and the reports should be broadly available through Her Majesties Stationary Office in the normal way.

SC + TECH · Underlay pt 10

ANDREW

Lynn Andrews called with reference to the ACOST meeting held last Wednesday and would like to know if you intend to make any changes to the minutes.

Parandoush

21/3

1. Mrs Slocock
2. CF

Qh 0638

File No. ST 310/2

MR TURNBULL
10 DOWNING STREET

March 16, 1990

cc Dr Bradley

ACOST COUNCIL 14 MARCH

1. I attach a copy of the minutes of the ACOST Council meeting chaired by the Prime Minister. I propose to circulate these on Monday 19 March but thought you would wish to have an advance copy.

C C Bradley

for JOHN REYNOLDS

Qh 0639

File No. ST 310/1 March 16, 1990

MR POWELL
10 DOWNING STREET

ACOST COUNCIL MEETING: 14 MARCH

1. I sent you a draft version of the minutes of the above meeting last night. Can you please replace these with the final version, a copy of which is attached.

C C Bradley

for JOHN REYNOLDS

Encl.

SCIENCE AND ENGINEERING RESEARCH COUNCIL

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Professor E W J Mitchell CBE FRS
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Dr Clive Bradley
ACOST Secretariat
Cabinet Office
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LONDON SW1A 2AS

Our Ref: P&S/AC/130

7 March 1990

Dear Clive,

SERC UNFUNDED ALPHA GRADED RESEARCH GRANT APPLICATIONS

1. We have recently taken a sample of about 10% of all unfunded alphas in the 4-year period 1985/86 to 1988/89, and followed them up with the 270 principal investigators involved.

2. Over the period the proportion of alpha graded applications funded was 59%. Of the 41% unfunded the answers showed that :

   a. 13 percentage points were funded on resubmission;

   b. 8 percentage points were funded by non-SERC sources;

   c. 20 percentage points were not funded.

3. I would be grateful if you could draw this to the attention of Lord Tombs.

Yours sincerely

Bill


16.00
PM90

cc Backup

PRIME MINISTER 9 March 1990

ACOST MEETING ON MARCH 14

1. Adaptive Biology

Both papers are fascinating and well worth reading in their entirety before the meeting if you have time. However, there is a dramatic assertion in the first paper by Harper which needs challenge. He suggests that a five degree centigrade rise over the next 50 years is "the firmest prediction" and that this will cause a world hotter than it has been since before the evolution of Homo Sapiens! This is over-dramatic because the scientific consensus is honing on a figure nearer 2° centigrade by the year 2050. See Annex 1 from Nature.

Annex 2, a recent paper from the AT&T Bell Laboratories, gives a thorough statistical analysis of the evidence for correlation between CO_2 increase and global warming. The most important paragraph (highlighted in yellow) is three from the end. CO_2 and temperature demonstrate correlation between 1958 and 1988 but the paper warns against the conclusion that there is a causal link. This work is useful in combatting the more hysterical arguments that the present climate problems are all part of greenhouse warming. John Mason would approve!

The Woolhouse paper on molecular biology has the greatest amount of meat. I found Section 4, which suggests that optimally fit organisms may have low adaptive capability, surprising and quite counter-intuitive.

2. The Science Base

This contains many platitudes with general assurance that all

is well. Nevertheless, there are a number of disquieting findings:

(i) The engineering board of SERC now absorbs 28% of total expenditure compared with 16% ten years ago. (Paragraph 20);

(ii) The report bemoans the high proportion of research council expenditure in councils' own establishments. This should not be in itself a cause of concern. The important question is the quality of the establishment. The Laboratory of Molecular Biology at Cambridge quite rightly absorbs a high proportion of MRC expenditure since it is among the finest organisations of its kind and produces many Nobel prizes;

(iii) The report is critical of the high proportion of funding going into dirigiste activity rather than the funding of individuals and new work. (Paras 20-23). You have often shown the same concern and it is a frequent theme of Max Perutz. The Report is bivalent because it then argues in Paragraph 35 that increased efficiency and better management must lead to larger teams!

This is a subject on which people are very confused, frequently arguing both sides at different times. Because certain kinds of modern research involve costly centralised equipment, its use must be rationed to organised teams. That should not however prevent the research itself being split horizontally. Individual workers will then have the creative freedom to generate and test new ideas in specific fields. The real danger is that the research becomes vertically grouped so that people are operating up and down a line rather like a chain of command in the army. It is that kind of

structure, where idea generation becomes a monopoly at the top of a tree, which must be fought not the existence of large teams per se;

(iv) The report identifies the ageing of academic staff. This is set out in figure 4.2 (ii) which is repeated in my Annexure 3 for convenience. Ten years ago only a third of university funded scientific academic staff were older than 45. Today this is more than 50 per cent which is disturbing and partly due to the system of tenured posts.

(v) DES Ministers frequently argue that there is no net brain drain because many overseas academics come to Britain. Paragraph 27 suggests that the quality emigrating is not matched by the quality coming in. This is obviously far more important than the balance of absolute numbers.

(vi) It is scandalous that over a third of laboratory equipment is more than 10 years old (paragraph 30). This may be because the academic community shows little self-discipline during times of stringency. It is far easier to cut expenditure on equipment than on people. Making universities accountable for UFC as well research council spending should help because the whole cost of a programme will be budgetted. There is no point in funding or continuing to fund a research project if the equipment is inadequate.

Expenditure on research equipment tends to rise higher than inflation because, as the science advances, more accuracy and more sophisticated tools are required. Therefore, a research budget which is constant in real terms, based on RPI deflators, may actually be declining

in terms of the research which can be done. There is no point in repeating this year's research next year!

3. **Advanced Manufacturing Technology**

This is a most disappointing paper full of the same old thinly disguised arguments for near market research funding by Government. Of course advanced manufacturing is important and, if industrial management does not recognise that, it will wither and be replaced, possibly through takeovers, by managements which which are responsive. But this is no argument for funding academics and DTI bureaucrats to show management how to run its business!

The best example of an advanced manufacturing research unit is Bhattacharyya's group at Warwick which you recently visited. I attach a strictly private letter from him arguing strongly against the ACOST Working Party recommendations. He states that it took no evidence from Warwick and suggests that its members other than the Chairman were all academics. His letter to me is attached at Annex 4.

5. **CERN - not on Agenda but an important part of science base.**

You might ask Christopher Llewellyn Smith, who will be attending ACOST for the first time, about recent developments at CERN now that the LEP (Large Electron Positron Collider) has been operating for six months. He is Chairman of the CERN Policy Committee and I am sure will be able to speak for a minute or two on recent achievements.

GEORGE GUISE

METEOROLOGY

Storm success came easy

London

THE UK Meteorological Office is this week congratulating itself for predicting successfully the hurricane-force gales which ravaged the British Isles on 25 January, leaving a trail of destruction and 47 dead. Strong winds were predicted when a deepening depression was picked up in the central Atlantic the previous weekend. When the pressure at the centre of the weather system began to plummet on the afternoon of 24 January, they forecast that a severe storm would hit the United Kingdom the next day, and warned that "structural damage is expected".

The Meteorological Office is keen to stress the accuracy and speed of its forecasts, following its failure to give similar warning of the storm that devastated southern England on 15–16 October 1987, claiming 19 lives. In 1987, the Meteorological Office's two forecasting models — a 'fine mesh' model, which gives detailed predictions, and a 'coarse mesh' model, which is less detailed but is updated more often — gave different results. This time, the models agreed, says Martin Morris, head of central forecasting.

In the wake of the 1987 storm, a report commissioned by the Ministry of Defence, which funds the Meteorological Office, concluded that training was inadequate and that senior forecasters were not afforded sufficiently high status. Since then, training has been extended and career structure overhauled. Televised weather forecasts now include more explicit storm warnings, and the system of notifying the emergency services has been streamlined.

But the nature of the storm, rather than changes in the Meteorological Office, provides the main reason for the difference in performance in 1987 and this year. Professor Brian Hoskins of the University of Reading explains that the 1987 storm did not have an obvious precursor in a marked depression, but was formed when several less obvious features came together. In its final approach to the English coast, the storm gained energy very rapidly as condensing rain released latent heat into the system. Morris says that the full potential of the 1987 storm became apparent only a few hours before it came ashore.

Not far from *Nature*'s London office, a tree felled in the 25 January storm. (AP)

This year's storm had a more leisurely and predictable development. Nevertheless, the occurrence of two hurricane-force storms over the English mainland within the space of three years raises the question of global climate change. Hoskins says that the storms were unusual, not in their intensity, but in their location. Usually, similar storms either 'blow themselves out' over the Atlantic, or pass over sparsely populated areas in northwest Scotland. He is currently examining the influence of greenhouse warming on storms, and believes that local shifts in storm paths are a possible consequence.

Peter Aldhous

CLIMATE CHANGE

New international projects planned

London

CLIMATOLOGISTS from Europe, the United States, Brazil and the Soviet Union meeting in Wallingford, Oxfordshire, earlier this week, agreed to increase the emphasis on long-term prediction of climate change in the International Geosphere Biosphere Project (IGBP) and the World Climate Research Programme (WCRP).

IGBP and WCRP are the two largest climate research programmes and the Wallingford meeting was of a joint committee aiming to coordinate efforts to improve the accuracy of general-circulation-model (GCM) predictions.

IGBP has chiefly been interested in the climatic effects of vegetation and greenhouse gases, whilst WCRP has concentrated on the interaction between the Sun's energy and the Earth's surface, and its effects on water relations. Climate prediction using GCMs requires complementary data from all of these areas.

Major studies agreed by the IGBP-WCRP committee include those on desertification in the Niger Sahel, deforestation in the Amazon basin, and of carbon cycling in the Canadian boreal forest. Peter Aldhous

CLIMATE CHANGE

Towards a 2°C concensus

Washington

EARLY signs of a scientific consensus on global warming emerged last week as top-level representatives from more than 40 countries prepared to gather in Washington next week for a meeting of the Intergovernmental Panel on Climate Change (IPCC).

Briefing a National Academy of Sciences panel on global change, a panel of atmospheric scientists agreed that significant effects from the greenhouse effect may now be considered "very probable." Although there was some disagreement on the magnitude of the expected temperature rise, almost all of the scientists briefing the academy believe mean global temperatures will go up by at least 2 °C by the middle of the next century. But the rise will not be uniform — the latest models show that the Northern Hemisphere, with a large land mass, will warm far more than the largely oceanic Southern Hemisphere.

Although the United States is not expected to announce any radical policy changes at the IPCC meeting next week, President George Bush may use the opportunity to highlight environmental features, such as a new $170 million tree-planting initiative, in his 1991 budget, which was released earlier this week (see p. 397). The administration is already touting a $500 million increase in global warming research funding for 1990, but most of that rise is due more to creative accounting than new money. Real increases in 1990 amount to about $60 million above 1989's $134 million research budget.

The administration may have to get its own house in order before it can hope to take a leading role on international global warming policy. The US government continues to be characterized by "inter-agency squabbling", according to Alan Miller of the University of Maryland's Center for Global Change. But with several European countries beginning CO_2 emission reduction programmes, the US administration risks falling out of step with international opinion on global warming. For that reason, President Bush has called for a White House meeting of top-level scientific and economic advisers from selected countries in the Spring. The meeting will help the Administration "determine where the uncertainties are in the science and economics of the issue", a White House spokeswoman says.

Congressional action may be on a faster track. In both the House and Senate, part of major bills to promote energy efficiency, emission controls, and reforestation are expected to pass this year.

G. Christopher Anderson

Coherence established between atmospheric carbon dioxide and global temperature

– see last page

Cynthia Kuo, Craig Lindberg & David J. Thomson

Mathematical Sciences Research Center, AT&T Bell Labs, Murray Hill, New Jersey 07974, USA

The hypothesis that the increase in atmospheric carbon dioxide is related to observable changes in the climate is tested using modern methods of time-series analysis. The results confirm that average global temperature is increasing, and that temperature and atmospheric carbon dioxide are significantly correlated over the past thirty years. Changes in carbon dioxide content lag those in temperature by five months.

DURING the past century (see, for example, refs 1, 2), scientists have studied the possibility that the climate is influenced by changes in the atmospheric concentration of CO_2 caused by industrial and agricultural activities[3–5]. Recently, because of the potentially serious consequences of the greenhouse effect[6,7], the problem has been studied more intensively[8,9] with a view towards observing climatic effects attributable to the increase of atmospheric greenhouse gases. For example, the output of numerical models of the global climate has been compared with measurements[10,11], and the significance of the temperature increase has been tested using various straight-line segment and parametric models (ref. 12 and J. Seater, manuscript in preparation). But present numerical models of the atmosphere are crude, and comparisons between the time series representing the real data and predictions of the atmospheric models are difficult to interpret. Because the available data are short time series, conventional statistical methods are unreliable, and detection of the greenhouse effect remains controversial[13–18].

The longest modern series of precise CO_2 concentration measurements begins in March 1958 and consists of monthly values collected by Keeling at the summit of Mauna Loa in Hawaii[19]. Although these data are from a single station, they are typical of measurements made since 1974 at several sites[20]. Because we are interested in the time-series aspects of the problem, we use the longer Keeling series. The data have an upward trend that is readily visible (the upper curve in Fig. 1), an obvious annual component and irregular fluctuations. Five missing values were interpolated using a stochastic least-squares procedure on the residuals from a quadratic polynomial plus the first five annual harmonics. These interpolated values have an estimated error of 0.35 p.p.m. and are noted in Fig. 1.

Hansen and Lebedeff[21] created a time series of monthly global-average surface-air-temperature changes from January 1880 to December 1988. This series is a weighted average over stations, formed by subtracting the average January temperature during the reference period 1951–80 from all the January data, and repeating this for the other months, eliminating seasonal variations. Displayed as the lower curve in Fig. 1, the temperature series also increases with time but its fluctuations are relatively larger than those in the CO_2 record.

Here we apply multiple-window time-series methods (which are efficient for short series) to estimate the trends and power spectra of the Hansen–Lebedeff average global surface temperature series and Keeling CO_2 concentration measurements as well as the coherence between the two. This analysis shows that from 1880 to 1988, the average global temperature increased by 0.0055 ± 0.00096 °C yr^{-1}, and the probability that this slope is positive exceeds 99.99%. Furthermore, the monthly CO_2 concentration and global temperature series from 1958 to 1988 are coherent over much of the Nyquist frequency band from 0 to 6 cycle yr^{-1}; the probability that the level of coherence observed from 0 to 2 cycle yr^{-1} occurred by chance is $\sim 2 \times 10^{-6}$. Not only do both series have increasing trends that are highly significant, but there are linear relations between many of their oscillatory components. We interpret this as evidence that the changes in atmospheric CO_2 concentration are closely related to changes in global temperature.

Models

Many of the contradictions in the literature about the analysis of climate data can be traced to the use of inappropriate or oversimplified models (for review, see, for example, refs 22, 23). Statistical techniques that are vulnerable to difficulties include those based on parametric models (such as low-order autoregressive moving-average representations) and methods plagued by more insidious problems caused by implicit assumptions of time-series stationarity. The cavalier use of parametric models can lead to misspecification difficulties[24] because

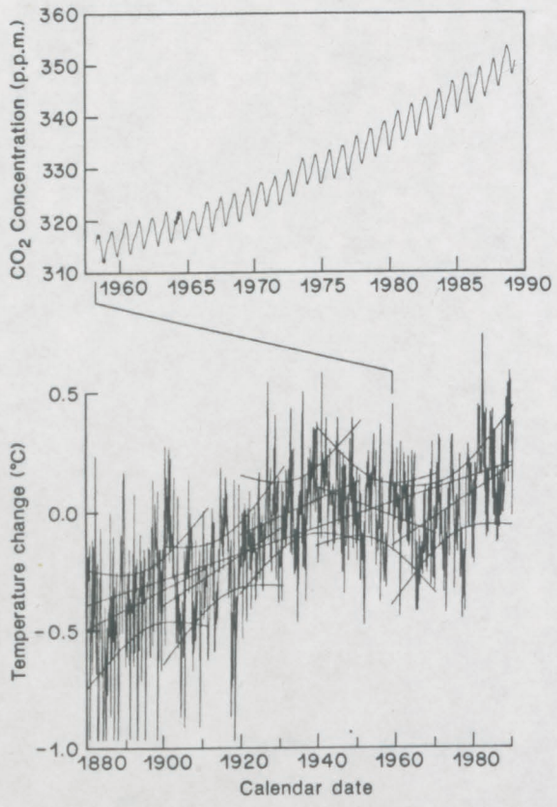

FIG. 1 The upper curve is the monthly Keeling CO_2 concentration data for March 1958 to December 1988. The five interpolated points are marked. The lower curve is the Hansen–Lebedeff average global temperature series for 1880 to 1988. The short line segments and hyperbolic arcs define trends and 95% confidence regions over 30-yr intervals, and the long straight line shows the general trend.

unanticipated effects (such as the modulation of the annual cycle discussed below) either are undetected, are attributed incorrectly or are simply lumped in as part of 'residual variance'. As shown below, the CO_2 concentration and global temperature series have complicated spectral density functions, so these series are not likely to be modelled by any simple form in either the time or frequency domains. The fundamental flaw of parametric models, including numerical atmospheric models and time-series models, is that they make no provision for the unexpected.

We represent each time series by the less restrictive decomposition into a parametric trend and a non-parametric residual. Because one cannot directly discriminate between the many possible functional forms for the trends from such short records, we represent the trend in each time series by the simplest non-constant function of time, a straight line of non-zero slope which can be thought of as the first two terms in the Taylor series expansion of the true trend. It may be argued that this semi-parametric representation is subject to the misspecification problems mentioned above, but, because we subject the residuals to greater scrutiny than we do the trends, features not included in the trends will still be present and studied in the residuals. Moreover, we find that including quadratic terms does not change the results of the following analysis significantly.

Therefore, we express each time series

$$\{x(0), x(1), x(2), \ldots, x(N-1)\}$$

as the sum of a constant, a linear trend and a stationary time series specified only by its spectral representation

$$x(t) = a_0 + a_1(t - t_{\text{ref}}) + e(t); \quad t = 0, 1, \ldots, N-1 \qquad (1)$$

where t_{ref} is a reference time, a_0 and a_1 are constants and the residual time series $e(t)$ has the spectral representation

$$e(t) = \int_{-1/2}^{1/2} e^{i2\pi ft}\, dX(f) \qquad (2)$$

for all t. $dX(f)$ is the differential of a generalized Fourier transform and is known as an 'orthogonal increment process'. (This is an extension of the representation used in ref. 25, where the CO_2 series was decomposed into a trend, an annual component and a residual.) The annual component is given by the first moment of $dX(f)$, and the power spectrum, or power spectral density, $S(f)$, of the residuals is, by definition, the second moment of $dX(f)$:

$$S(f)\, df = \mathbf{E}\{|dX(f)|^2\} \qquad (3)$$

where $\mathbf{E}$ is the statistical expected-value operator. In a stationary series, values of $dX(f)$ at distinct frequencies are uncorrelated[26].

Estimation

Although the time- and frequency-domain representations of time series are formally equivalent[27], we usually find it more informative to analyse time series in the frequency domain where the effects of different physical processes can be easier to distinguish. With short time series, such as the CO_2 and global temperature records, it is difficult to resolve different frequencies and simultaneously obtain statistically significant results. Our approach is to use a variant of the multiple-window method of spectrum analysis[28,29] that, although it does not eliminate all the problems associated with short series, makes statistically efficient use of the available data.

Most frequency-domain methods are strictly valid only for the analysis of stationary data, not series with embedded trends such as the CO_2 and global temperature records. Using the multiple window procedure described below, we estimate the trends in each series, subtract off these terms, and estimate the spectrum of the residuals. Finally, we test the residuals for stationarity to see if our assumptions were violated.

Estimating the average a_0 and trend a_1 by ordinary least squares can produce misleading results if the residuals $\{e(t)\}_{t=0}^{N-1}$ have a non-white (non-flat) spectrum and are therefore correlated[30,31]. The residual spectrum need only be roughly flat in a small frequency interval around the origin for multiple-window regression, however, to produce valid estimates of a_0, a_1, the spectrum of the residuals and their errors.

Multiple windows

The multiple-window method uses the orthogonal sequences of N elements that optimally concentrate the spectral energy in a frequency band of width $2B$ centred on a frequency f, that is, between the frequencies $f-B$ and $f+B$. These sequences are the lowest-order $\lfloor 2BT \rfloor$ discrete prolate spheroidal sequences of ref. 32, where T is the duration of the observed series. These 'Slepian sequences' form a basis on which the data in the

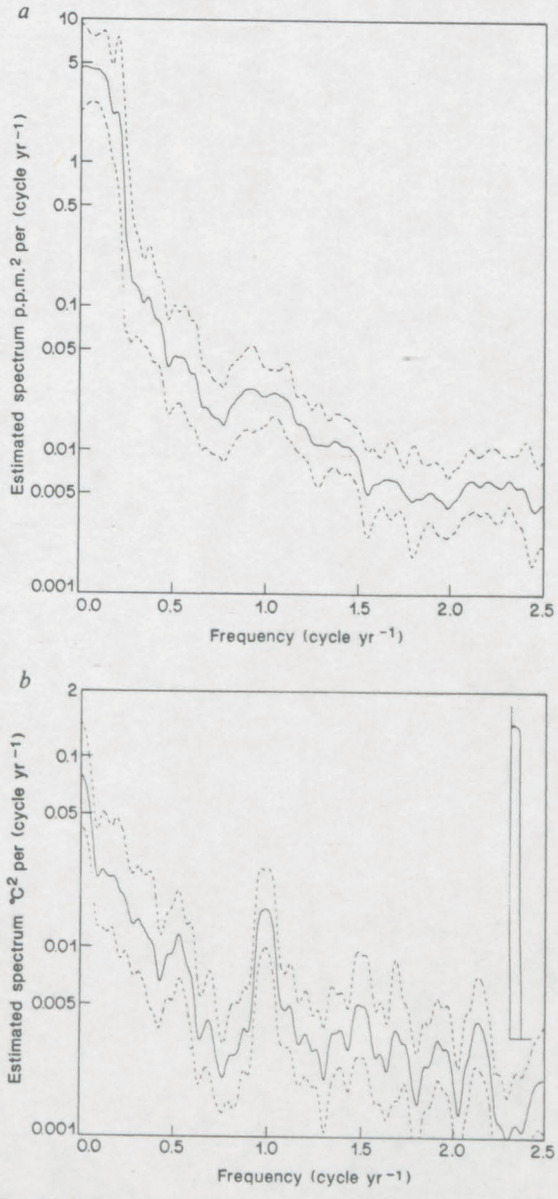

FIG. 2 *a*, Multiple-window spectral estimate of trend-subtracted CO_2 concentration series. The upper and lower dashed curves are 5 and 95% confidence limits obtained by jackknifing on the windows. Harmonics of the annual cycle have been subtracted. *b*, Multiple-window spectral estimate of detrended global temperature series for the interval 1880 to 1988. The dashed lines give the 5 and 95% confidence intervals as in *a*. The insert on the upper right shows the effective spectral window on the same amplitude and frequency scale. Note that the power around 1 cycle yr^{-1} is not a periodic component. (Spectra done at higher resolution show that this feature is asymmetric with more power on the lower sideband than on the upper, indicating combined amplitude and phase modulation of the annual cycle.)

frequency band can be expanded. The coefficients of this expansion depend on frequency and are obtained by taking the discrete Fourier transform of the product of the data with each Slepian sequence. The lowest-order coefficient is similar to a direct spectrum estimate using a conventional data window or taper. A multiple-window estimate of the spectrum is, however, an adaptively weighted average of the $2BT$ frequency-dependent coefficients.

Because of their energy-concentration properties, the Slepian sequences are the data windows that are most resistant to spectral leakage[28]. For example, the estimate of the temperature-series spectrum in Fig. 2*b* is produced using 11 Slepian sequences with $2B = 0.11$ cycle yr^{-1}; sidelobes of the effective spectral window shown in the insert are unobservable on the scale of Fig. 2*b*.

Choosing the parameter B for a multiple-window estimate of a spectrum involves a tradeoff between resolution and variance. The variance of this spectrum estimate is proportional to $1/(2BT)$. Thus, increasing B improves statistical reliability but decreases the resolution of the estimate.

Trend estimates

To estimate the coefficients a_0 and a_1 in equation (1) by conventional time-domain regression, one minimizes the sum of the squares of the residuals $\sum_{t=0}^{N-1} e^2(t)$ with respect to the coefficients. By Parseval's formula,

$$\sum_{t=0}^{N-1} e^2(t) = \int_{-1/2}^{1/2} |\tilde{e}(f)|^2 \, df \tag{4}$$

where $\tilde{e}(f)$ is the discrete Fourier transform of the residuals $\{e(t)\}_{t=0}^{N-1}$, so minimization in either the time or frequency domain is equivalent. To avoid the energy associated with the harmonics of the annual cycle and other high-frequency processes, however, we minimize only the integral over the low frequencies

$$\int_{-W}^{W} |\tilde{e}(f)|^2 \, df; \quad W = BT/N < \tfrac{1}{2} \tag{5}$$

and ignore the higher-frequency components of the residuals, resulting in estimates expressible in terms of the Slepian sequences.

The multiple-window approach has several advantages when the residuals are autocorrelated. First, the 'observations' in the multiple-window regression are closer to independent gaussian random variables than the original time-domain data $\{x(t)\}_{t=0}^{N-1}$, and therefore the multiple-window coefficient estimates are closer to maximum-likelihood estimates than are the estimates from ordinary least-squares analysis. Similarly, the number of degrees of freedom and error estimates are easily calculated using the Slepian sequences, and the multiple-window method is often more statistically efficient than ordinary least-squares analysis (C. Lindberg, manuscript in preparation). In conventional regression, the endpoints of the time series (for example, the abnormally high temperatures of the last decade) can have an inordinately large influence on the coefficient estimates[33]. This effect is largely eliminated in this approach. Finally, it is relatively easy to check the assumptions that have been made in representing the data by a particular model.

Trends

For the monthly Keeling CO_2 series (March 1958 to December 1988, $T \approx 29.8$ yr), estimates of the average and trend were obtained using $t_{ref} = 1975.0$, and a bandwidth of $2B = 0.39$ cycle yr^{-1}. This value of B confines the spectral energy associated with the trend components to frequencies f with $|f| \leq 0.195$ cycle yr^{-1}, avoiding energy associated with the annual cycle and its harmonics. This value of B also results in a spectrum that is locally white in the resolution band (at frequencies above 0.2 cycle yr^{-1}, the CO_2 residual spectrum drops rapidly, as shown below). The time-bandwidth product $2BT \approx 11.6$ gives eleven leakage-resistant windows. The multiple-window procedure results in the estimates $a_0 = 331.9 \pm 0.44$ p.p.m. and $a_1 = 1.191 \pm 0.053$ p.p.m. yr^{-1}.

For the monthly Hansen–Lebedeff global temperature series from January 1880 to December 1988, we obtained estimates of the average and trend using $t_{ref} = 1934.5$ and a resolution bandwidth of $2B = 0.128$ cycle yr^{-1}. This value of $2B$ was chosen to avoid the frequency band above 0.07 cycle yr^{-1} where the residual global temperature spectrum decreases rapidly, as shown below. Using 12 Slepian sequences, we obtain $a_0 = -0.106 \pm 0.030$ °C and $a_1 = 0.00554 \pm 0.00096$ °C yr^{-1}.

For comparison, estimates from ordinary least-squares analysis agree with the multiple-window estimates to three significant figures but, because of the lower values of the spectrum at higher frequencies, underestimate their standard deviations by a factor of five.

To assess the significance of this estimated global temperature slope, we note that Milankovitch theory predicts that at present the Earth should be cooling by ~ 0.0004 °C yr^{-1} (refs 34, 35). Thus, solar variability aside, the null hypothesis is that the temperature trend should be slightly negative. To test this hypothesis we use a t statistic $t = [0.00554 - (-4 \times 10^{-4})]/0.000961 = 6.18$ which, as 12 windows were used and two parameters were estimated, is characterized by approximately 10 degrees of freedom. Therefore, given that the low-frequency spectrum is approximately white (see Fig. 2*b*), the slope is greater than the Milankovitch prediction with probability 99.995% (ref. 36). Using a narrower bandwidth leads to fewer Slepian sequences with resistance to spectral leakage, fewer degrees of freedom and an underestimate of the slope significance. A wider bandwidth results in an invalid t statistic, as the residual spectrum decreases rapidly at frequencies >0.07 cycle yr^{-1} and so violates the 'locally white' assumption. Neither a jackknife variance estimate[37] (a non-parametric statistic sensitive to both non-gaussianity and non-stationarity, determined from the set of spectrum estimates computed with each of the windows deleted in turn), nor the stationarity test of ref. 38 show the residual series to be non-stationary. High-resolution quadratic inverse spectrum estimates provide some evidence for a ripple on the spectrum at frequencies <0.07 cycle yr^{-1}, consistent with a 'recurrence time' in the temperature data of ~ 28 yr, but the amplitude of this ripple is not enough to change the significance of the slope.

Finally, it has been argued that the negative trend in the temperature record between 1940 and 1970 invalidates the conclusion that the temperature is increasing over the long term. To test this, we repeated the trend calculations for overlapping 30-year subsections of the Hansen–Lebedeff series. The estimated trends for each interval are shown as the short straight lines through the temperature record in Fig. 1, and the 95%-confidence region of each is bounded by the hyperbolic arcs[39]. The line associated with the linear trend of the entire temperature record remains in the corridor collectively outlined by the subsection error bounds.

Spectrum estimates

We estimate the spectrum of the residual series $\{e(t)\}_{t=0}^{N-1}$ by subtracting the periodic components (detected by a statistical F-test[28]) from the detrended data, and by making an adaptively weighted multiple-window estimate of the power spectral density $S(f)$ of the residuals[28]. No frequency components above 2.5 cycle yr^{-1} are shown to avoid artefacts from the unequal lengths of the months.

Figure 2*a* is the low-frequency part of the spectrum estimate of the CO_2 residuals using $2B = 0.39$ cycle yr^{-1} and 11 windows. The spectrum is not white, so estimates using ordinary least-squares analysis of the CO_2 trend error bounds are invalid. The variance of the estimate has been calculated by jackknifing over windows[37,40,41], and the resulting 5% and 95% confidence limits are shown. These error bounds are consistent with the

χ^2 distributed estimate (with 22 degrees of freedom) expected from stationary gaussian data. Because of the shortness of this series, it is unlikely that details in the low-frequency end of the spectrum have been resolved; the plotted spectrum is a compromise between frequency resolution and statistical significance.

Figure 2*b* shows an estimated spectrum of the Hansen-Lebedeff global average temperature residual series. To allow resolution of more details in the spectrum, a bandwidth of $2B = 0.11$ cycle yr^{-1} was used, resulting in 11 Slepian sequences

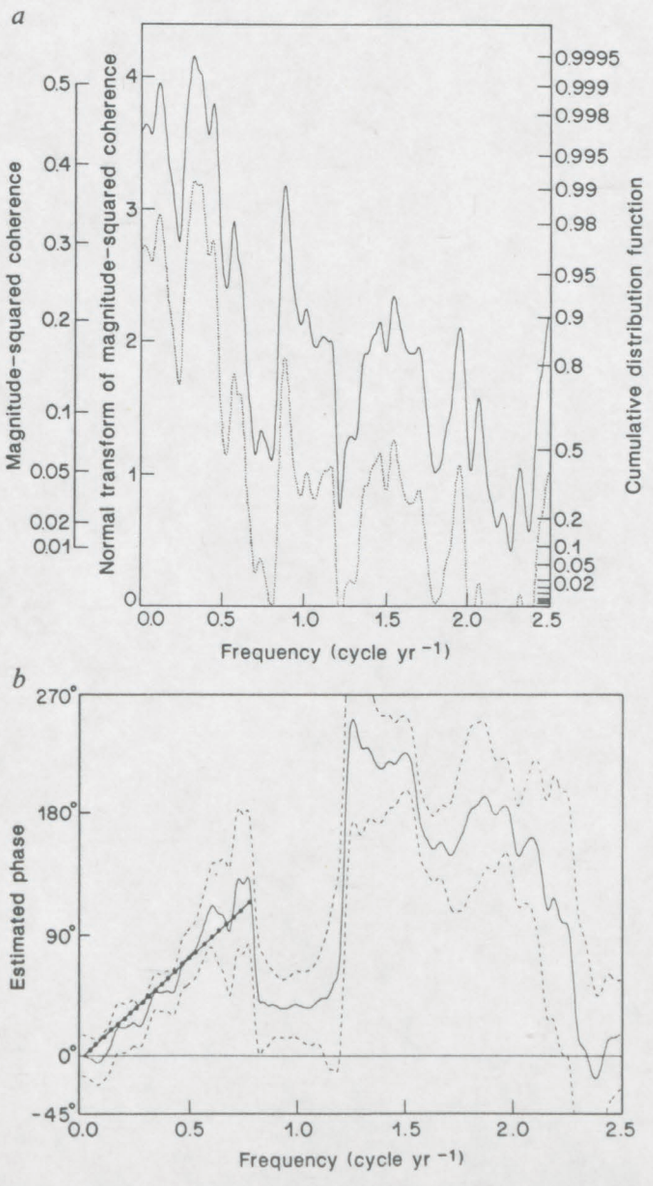

FIG. 3 *a*, Magnitude-squared coherence (MSC), between the Keeling CO_2 series and the global temperature series during 1958–1988. The vertical axis on the far left is the value of the MSC, and the axis on the left of the graph is the value of the coherence magnitude transformed by $\tanh^{-1}$. On this scale the coherence estimates should be roughly gaussian with unit standard deviation[49]. The vertical axis on the right gives the cumulative distribution function for incoherent series. The upper (solid) curve represents the transformed coherence values $\{\tanh^{-1}(|C(f)|)\}$, and the lower (dashed) curve is offset by one standard deviation as determined by jackknifing over windows. *b*, Phase of coherence between the Keeling CO_2 series and the global temperature series during 1958–1988 corresponding to the MSC in *a*. The two dashed lines show the ±1 s.d. limits obtained by jackknifing. The low-frequency trend in the phase corresponds to a delay of ~5 months, whereas the 'hole' near 1 cycle yr^{-1} reflects the predominance of other effects near this frequency. The poorer limits on the phase at higher frequencies is a consequence of the lower coherences there. These jackknife estimates agree with gaussian theory.

($2BT = 108 \times 0.11 = 11.88$). As noted in ref. 21, this spectrum exhibits substantial power at periods near integer multiples of the annual cycle. Because the *F*-test shows that this power is not a simple periodic signal in the data (recall that the Hansen-Lebedeff referencing procedure has already subtracted the annual cycle) we examine it further below.

Relations between the series

That both the CO_2 and global temperature data have positive slopes does not prove that the two series are related. As the discussion on spurious correlation in ref. 42 makes clear, the presence of the trends in each series will cause simple time-domain correlations between the two series to be high. If it is found, however, that the fluctuations of the two detrended series are coherent over a band of frequencies, then it is more likely that the two series are related.

The frequency-domain analogue of correlation, coherence[43–45], has been applied to meteorological data for many years[46]. Conventional estimates of coherence between single sections of two records are the smoothed (by a moving average) complex product of the discrete Fourier transforms of the two series, and so can be badly biased if the phase changes over the averaging band. Section-averaging methods are inappropriate for short series; not only does dividing these series into subsections result in poor frequency resolution, but the correlation between the subsections produces unreliable coherence estimates. The multiple-window approach described in refs 28 and 41 provides a less biased estimate of coherence $C(f)$ which is suitable for short series, allowing the extraction of more information from the same data.

Figure 3*a* shows the multiple-window magnitude-squared coherence between the Keeling CO_2 and global temperature residuals from 1958 to 1988 (produced using the same bandwidth and number of windows as the spectrum estimate of the CO_2 residuals). It is remarkable that the two series have a coherence above the 90% confidence level at frequencies <0.6 cycle yr^{-1} with coherence exceeding 98% over much of this low-frequency band. Because multiple-window coherence estimates spaced $2B$ apart are essentially independent, the probability of observing such levels across a wide band by chance from independent series is very low, $\sim 2 \times 10^{-6}$. Thus, not only are the trend components (at frequencies ~0 cycle yr^{-1}) of both time series increasing, but the residuals of the two series are also coherent with high confidence in the low-frequency band.

Figure 3*b* is a plot of the phase of the multiple-window coherence between the two residual (trend-subtracted) series. The phase of the coherence at 0 cycle yr^{-1} is zero and, because both trends are positive, is independent of whether trends are included or not. Between 0 and 0.8 cycle yr^{-1} the phase is roughly linear, corresponding to the CO_2 series lagging the temperature series by ~5 months (calculated by taking the slope of this linear section of the phase[44], $\sim 120°/(360° \times 0.8$ cycle yr$^{-1})$) in agreement with arguments that natural positive feedback mechanisms in the carbon cycle causes carbon dioxide to lag temperature in some frequency bands[19] (R. Marston, personal communication). Current knowledge of these complicated interactions involving solar forcing, the Southern Oscillation and exchange of CO_2 with the oceans on various timescales, is summarized in section 6.6 of ref. 19. Also, in agreement with Keeling's hypothesis that ocean processes are dominant, we find that the coherence between the CO_2 and the Southern Hemisphere average temperature records is slightly higher than that for the Northern Hemisphere and that the observed delay of ~5 months between the global temperature and CO_2 is also seen in the Southern Hemisphere phase. As the Northern Hemisphere average temperature leads CO_2 by ~3 months, part of the ~5-month delay must be due to the transport time from the Southern Hemisphere to Mauna Loa.

The hole in the phase curve near 1 cycle yr^{-1} occurs because the temperature spectrum there is dominated by a different

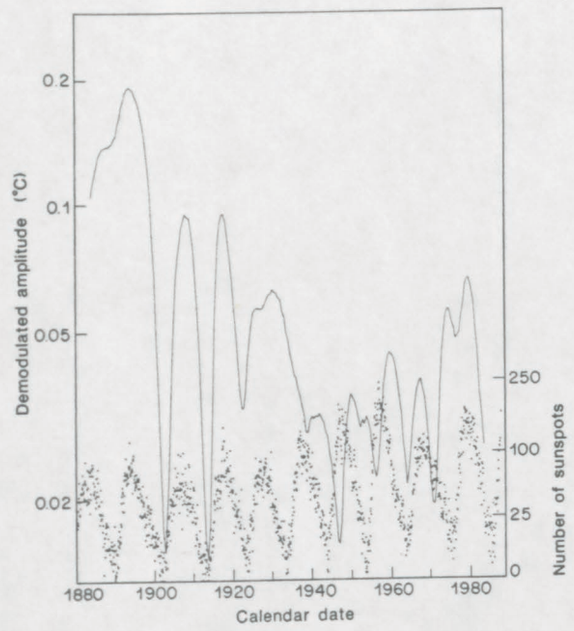

FIG. 4 The solid curve shows the amplitude of the complex demodulate of the Northern Hemisphere temperature record between 0.9 and 1.1 cycle yr^{-1}. A plot of the sunspot numbers is shown below. Detailed examination of the coherence between the demodulate and the solar cycle shows that these two have about a 1/(30 yr) difference in frequency (corresponding to the stronger lower sideband mentioned in Fig. 2*b*).

physical mechanism, and because of their different phase characteristics, we analyse the Northern and Southern Hemisphere temperature records separately in this frequency band. To do this, a multiple-window bandpass-filtered temperature series is formed by expanding the residual temperature series on a set of Slepian sequences that have most of their spectral energy confined between 0.9 and 1.1 cycle yr^{-1}. The resulting 'complex demodulate' for the Hansen–Lebedeff Northern Hemisphere temperatures is shown by the solid line in Fig. 4. The sunspot record (solid dots in Fig. 4) is clearly similar to the demodulated temperature data, suggesting that the annual signal is modulated by fluctuations in solar output. Detailed analysis shows that coherence between the sunspot and filtered temperature series is significant, and similar to the non-stationary structure found in ref. 47. The phase of the sunspot-filtered temperature coherence has a linear drift, corresponding to a frequency difference between these two oscillations of $1/\Delta$, where $\Delta = 27$–30 yr, possibly related to the low-frequency ripple in the temperature spectrum mentioned above. The results for the Southern Hemisphere are similar.

Discussion

The coherence results presented here provide significant evidence that the average global temperature and CO_2 concentration from 1958 to 1988 are linearly related at many frequencies. But caution must be exercised in interpreting this result as suggesting that the variations in atmospheric CO_2 are causing the changes in global temperature, even though there are plausible physical mechanisms linking the two series. Apparent correlations that are used to postulate causality can sometimes be misleading, as in the case involving timing of earthquakes[48]. In addition, one should be particularly cautious in interpreting the coherence when the series analysed are as short as these; climatic and solar variations often are of longer duration than these records.

From atmospheric chemistry, global temperature depends nonlinearly on CO_2 concentration (T. Graedel, personal communication). The procedure used here implicitly uses a linear dependence. Bispectral estimates provide evidence of quadratic terms, although the shortness of these series makes this difficult to quantify. Also, except for the solar modulation of the temperature series near 1 cycle yr^{-1}, we have ignored the cyclostationary properties of these two series (that is, the statistics of these series vary periodically).

A more complete analysis would include estimates of the coherences between the various global average temperature time series, records of atmospheric CO_2 concentration, human CO_2 production, sunspots, volcanic activity and the Southern Oscillation Index, which are all high in various frequency bands and have complicated phase interrelations. For example, the coherence between the detrended Keeling CO_2 series and the Southern Oscillation Index is high near 0.4 and 2.4 cycle yr^{-1}. If we calculate the coherence between the CO_2 and global temperature series from which terms describing their linear dependences on the Southern Oscillation Index and sunspot record have been subtracted (called a partial coherence), the low-frequency magnitude-squared coherence increases to almost 0.7 whereas it decreases near 0.3 cycle yr^{-1}. Several of these series also exhibit an oscillation at an apparent period of ~15 years. Further analysis of their multivariate relations will be described elsewhere in more detail. □

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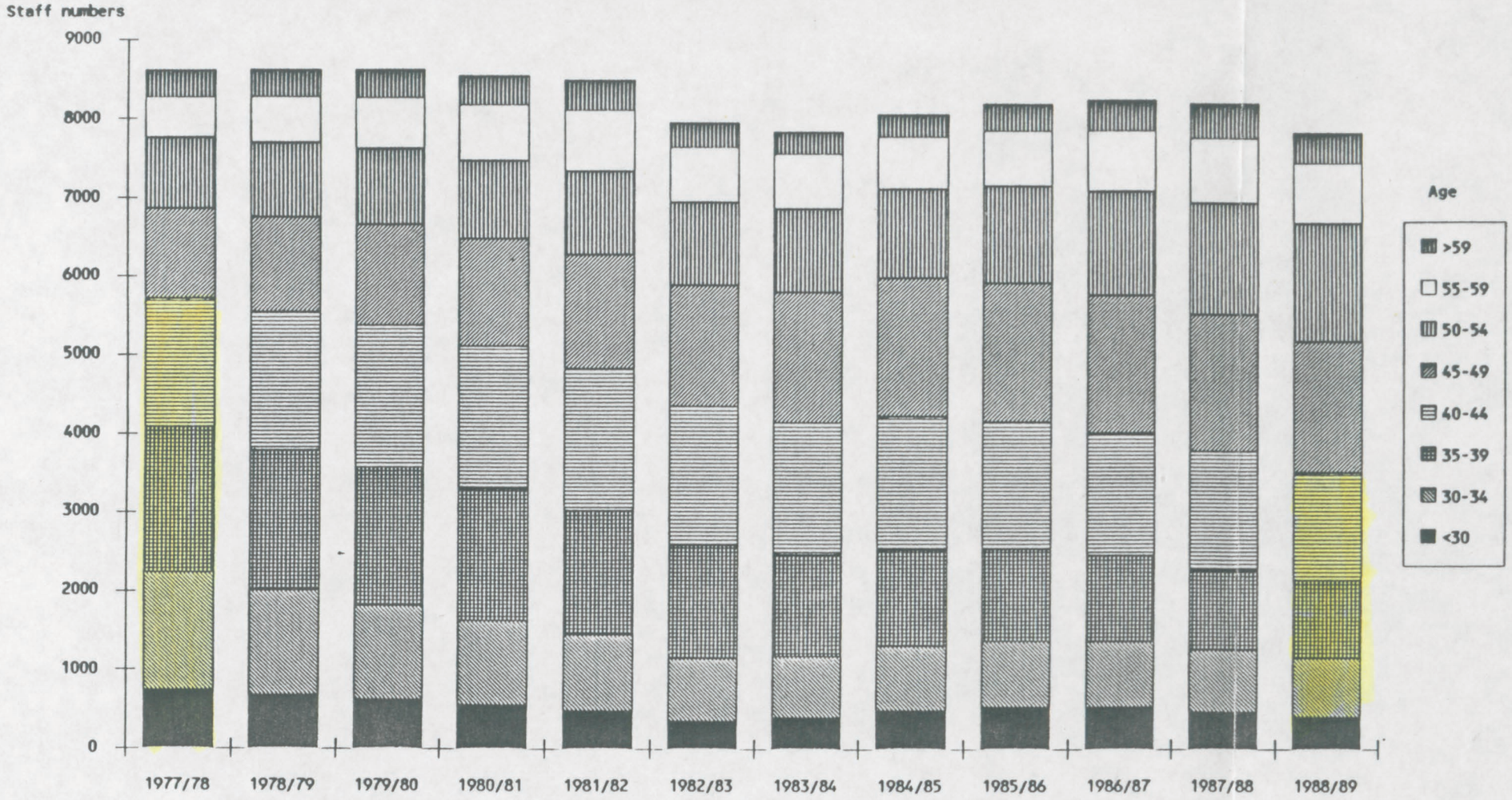
ANNEX 3

Figure 4.2(ii) Age profile of academic staff: science, wholly university funded



ANNEX 4

DEPARTMENT OF ENGINEERING

PROFESSOR S.K. BHATTACHARYYA, B.Tech., M.Sc., Ph.D., C.Eng., M.I.Mech.E., F.I.Prod.E., F.B.I.M.
Lucas Professor of Manufacturing Systems

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PRIVATE AND CONFIDENTIAL

SKB\SKB14\mb

8th March, 1990

Mr G Guise
Policy Unit
10 Downing Street
LONDON
SW1A 2AA

Dear George

ACOST and Advanced Manufacturing Technology

I have been led to believe that the next ACOST meeting will consider a report from a working party on Advanced Manufacturing Technology. One of the major recommendations will be to set up a skills centre for training and research.

If the recommendation is accepted, it is likely to lead to a request for pump-priming funding from Government.

I attach a confidential note to explain why I think that this is an example of 1970's thinking and why a new centre is not needed.

Yours.

.....

S.K. Bhattacharyya

Centre for Advanced Manufacturing Technology

"Advanced Manufacturing Technology" is not, in fact, a single technology. The subject is really about all the multitudinous ways that a company uses modern technology to remain competitive. It is all-pervasive.

Training and research are vital but, because the subject is the life-blood of manufacturing companies, they should be taking the lead. They should be equipping in-house or external centres and bearing the brunt of the training costs.

Where there has been a big input from public funds to equip universities and other organisations, they have never weaned themselves off continued public support, much of it coming from DTI.

Examples are the old Machine Tool Industry Research association (MTIRA), the National Engineering Laboratory and the Production Engineering Research Association (PERA). SERC is also funding a good deal of near-market development in Universities. Major equipment has been installed and not updated. There have been technology-transfer gaps between the publically-funded bodies and industry, hence the Government's own thrust for privatisation of research associations and national laboratories. At the lower end of the training spectrum, what has happened to the Skills Centres and their huge public investment?

Where companies themselves have taken the lead, for example at Warwick, the story is different. Of our annual turnover of nearly £10M for training and research in manufacturing systems, only 9% comes from the Government (predominantly from UFC for undergraduate teaching and the remainder from SERC). Nearly 3,000 company staff from manufacturing companies attend development courses each year. The latest facilities and equipment are made available, and are kept up-to-date, at no cost to the public purse. A list of partner companies is attached.

If industry needs more provision than currently exists in the UK, then it should have started it. Conversely if the academics believe that larger programmes are needed why have they not created them already? I believe that, other than the Chairman, all the members of the Working Party on Advanced Manufacturing Technology are academics.

The Working Party has not taken any evidence at Warwick and may not be aware of what has already been achieved with industry. I do not see how they could come to their views if they had seen at first hand what has been achieved here.

It might be argued that, although the good companies have exploited advanced manufacturing to gain a competitive edge, there are mediocre companies that need public subsidy through a skills centre to do so. I suggest that it is not ACOST's role to advocate propping up unsuccessful companies. I am personally surprised that ACOST has even tackled such a topic, which is properly the business of industry and not of Government.

In short, the Working Party recommendation smacks of an academic-biased plea that "the Government should do something" and of DTI officials yearning for the good old days of intervention. (I understand that the DTI has not been able to spend its money on advanced manufacturing research).

In practice, the existing support mechanisms through SERC and DTI have been sufficient to allow Warwick to create an industrially-funded centre. There are other University examples, not as large and often dominated by one or two equipment suppliers rather than our multi-supplier approach, but still good examples of how the new freedoms have been exploited.

I believe that there is no case for public funds to equip a new skills centre.

DETAIL ABOUT WARWICK

MANUFACTURING SYSTEMS ENGINEERING GROUP

The Group is the largest part of the Engineering Department and has a five-star research rating.

Of its 140 staff, over 110 are supported by external income. This is a unique proportion among UK institutions. Other distinguishing hallmarks are:-

- all postgraduate education and research is joint with companies;
- the vast majority of staff are on non-tenured contracts (this is not a recent change, it goes back to the Group's foundation in 1980);
- all staff are on continuous assessment;
- generation of a sizeable financial surplus for the University.

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Currently there are over 400 young men and women from 37 companies on the Masters Degree programme. Each year over 2,500 senior and middle managers are on executive development courses.

The courses are devised, taught and assessed jointly with the Companies. In fact 60% of the course material is taught by them; the MSE Group believes hat no University department should expect to retain a monopoly on new knowledge of a wide enough spectrum to satisfy industry's fast-changing needs.

The partnership extends into the research programme where the Group has a number of joint research centres sponsored by companies:

- Computer Aided Design Centre
- Centre for Manufacturing Renewal, specialising in dealing with small companies
- Computer Simulation Centre
- Computer Integrated Manufacturing Facility
- Catalysis and Surfaces Laboratory
- Advanced Technology Centre

The total industrial funding for training and research, including provision of state-in-the-art facilities, is in excess of £25M. In addition there has been pump-priming support from SERC and DTI for Teaching Companies, the graduate development programme, and research grants.

The list of partner companies includes:

Automotive and Component Sectors

Rover	Jaguar	GKN
Lucas	Rearsby	J. Marshall Engineers
Dynacast International	Leyland-Daf	Bajaj Auto
Timken	HDA Forgings	Ind Suzuki
Brose	SP Tyres	

Aerospace Sector

Rolls-Royce	British Aerospace	Short Brothers
Westland	Dunlop Aviation	Plessey Aerospace
British Airways		

Computing and Automation Sector

Digital	Prime	Asea Brown Boveri
Cincinnati Milacron	Allen-Bradley	ISTEL
John Brown Automation	Matra Datavision	ICAD
Symbolics		

Other Sectors

Vickers Shipbuilders	Thorn EMI	BICC Cables
IMI Refiners	Wedgewood	Norcross
Potterton	Coopers & Lybrand	Unilever
Shell	Kratos	Schlumberger
Du Pont	Raychem	

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Currently there are over 400 young men and women from 37 companies on the Masters Degree programme. Each year over 2,500 senior and middle managers are on executive development courses.

The courses are devised, taught and assessed jointly with the Companies. In fact 60% of the course material is taught by them; the MSE Group believes hat no University department should expect to retain a monopoly on new knowledge of a wide enough spectrum to satisfy industry's fast-changing needs.

The partnership extends into the research programme where the Group has a number of joint research centres sponsored by companies:

- Computer Aided Design Centre
- Centre for Manufacturing Renewal, specialising in dealing with small companies
- Computer Simulation Centre
- Computer Integrated Manufacturing Facility
- Catalysis and Surfaces Laboratory
- Advanced Technology Centre

The total industrial funding for training and research, including provision of state-in-the-art facilities, is in excess of £25M. In addition there has been pump-priming support from SERC and DTI for Teaching Companies, the graduate development programme, and research grants.

The list of partner companies includes:

Automotive and Component Sectors

Rover	Jaguar	GKN
Lucas	Rearsby	J. Marshall Engineers
Dynacast International	Leyland-Daf	Bajaj Auto
Timken	HDA Forgings	Ind Suzuki
Brose	SP Tyres	

Aerospace Sector

Rolls-Royce	British Aerospace	Short Brothers
Westland	Dunlop Aviation	Plessey Aerospace
British Airways		

Computing and Automation Sector

Digital	Prime	Asea Brown Boveri
Cincinnati Milacron	Allen-Bradley	ISTEL
John Brown Automation	Matra Datavision	ICAD
Symbolics		

Other Sectors

Vickers Shipbuilders	Thorn EMI	BICC Cables
IMI Refiners	Wedgewood	Norcross
Potterton	Coopers & Lybrand	Unilever
Shell	Kratos	Schlumberger
Du Pont	Raychem	

COVERING CONFIDENTIAL

W0399

MR GREY

9 March 1990

ACOST MEETING TO BE HELD ON 14 MARCH AT 1500hrs
CONFERENCE ROOM A, CABINET OFFICE.

I attach a brief for the meeting which the Prime Minister will chair.

SIR JOHN FAIRCLOUGH
Chief Scientific Adviser

CONFIDENTIAL

PRIME MINISTER

BRIEF FOR ACOST MEETING: 14 MARCH 3.00 PM

ATTENDANCE

1. A list of those attending is at FLAG A and a seating plan at FLAG B. Lord Chilver and Mr David McMurty will not be attending; they send their apologies.

INTRODUCTIONS

2. Lord Tombs will introduce the ACOST members appointed since your last attendance on 1 February 1989 and the two invited speakers:

New Members (1st meeting, July 1989.)
Professor Roy Anderson
Dr Peter Doyle
Mr Ian Harvey
Professor Gareth Roberts
Sir Alfred Shepperd
Professor Christopher Llewellyn Smith
[Lord Chilver - not attending]

Invited Speakers
Professor John Harper
Professor Harold Woolhouse

He will then invite you to take the chair.

AGENDA AND PAPERS

3. The Agenda is at FLAG C and the papers for agenda items 2, 3 and 4, together with synopses are at FLAGS D,E and F respectively.

AGENDA ITEM 1: CHAIRMAN'S OPENING REMARKS 3.00-3.05

4. You may wish to open with the following general remarks:

i. I would like to thank ACOST for their advice and reports which have informed our policy decisions on science and technology over the last year. Perhaps I could make special mention of the Committee's timely and very useful input to the Government's consideration of new EC Framework Programme. I know that ACOST's report on this was put together within a very tight timetable.

ii. I found the seminar with young research scientists in September stimulating and very enjoyable. We must ensure that our best young people are given the support and encouragement they need. One aspect which surprised me was the relatively low proportion of their funding coming from the Science Base. Perhaps we could look at this under agenda item 3.

iii. On the same subject, I am pleased that the Government has been able to increase the science budget for 1990/91 by a further £60 million. The Chancellor's announcement in his Autumn Statement of this additional 8% [over 1989/90] means that, since 1979 the science budget will have gone up by over 27% in real terms.

iv. I welcome the formation of ACOST's Standing Committee on the Environment. In this area Government needs a much fuller understanding of the relative merits of the policy options available. Proposed action to ameliorate one environmental problem invariably affects others. We lack comparative information on the full consequences of alternative strategies and I look forward to the Committee's advice in this area.

ITEM 2: ADAPTIVE BIOLOGY 3.05-3.40

Paper - AST(90)10, Adaptive Biology
+ synopsis at FLAG D

Background

5. ACOST has recently established an Environment Standing Committee chaired by Professor Roy Anderson. The Committee will concentrate on the impact of environmental issues and will undertake its work with the assistance of Research Programme and Economic Questions working groups.

6. ACOST has commissioned the 2 papers on Adaptive Biology annexed to AST(90)10. Both consider environmental issues. However, they are papers from individuals, Professor Harper and Professor Woolhouse and do not necessarily reflect the views of the community.

7. The ACOST Standing Committee, at its first meeting on 26 February discussed the papers and majored on issues concerning gene banks, temperature responses, CO_2 concentration and molecular biology. ACOST will wish to discuss these further in order to give the Standing Committee a steer on how to proceed.

Handling

8. The invited speakers, Professor John Harper and Professor Harold Woolhouse will each give a ten-minute presentation before the general discussion. They are due to leave before the next agenda item is considered.

9. We know that the following would like to contribute to the discussion:

- Professor Roy Anderson (Chairman, Environment Committee)
- Sir George Porter
- Professor Keith Peters
- Mr Ian Harvey
- Professor Thomas Blundell
- Dr Peter Doyle

10. OUTCOME - Identification of priorities for consideration by the Environment Committee.

Points for Discussion

11. You may like to emphasise that the study of adaptive biology is of strategic importance in its own right, even if there is no greenhouse effect. Adaptation relies on the natural variation within and between species. The exploitation of this diversity, underpinned by understanding at the molecular level, will lead to wealth creation in food, agriculture, chemicals, pharmaceuticals, waste disposal, etc. The UK already has a strong presence and the broad question is how we can capitalise on this.

If you have time, this paper is worth reading in full
AT

ITEM 3: INTERIM REPORT OF THE SCIENCE BASE GROUP 3.40-4.05

Paper - AST(90)11, Revised Interim Report of the Science Base Group + synopsis at FLAG E
N.B. The Annex to AST(90)11 is separate

Background

12. AST(90)11 is an interim report. ACOST will be considering what steer to give to the Group.

13. The report is positive and emphasises that the Science Base has received increased funding in real terms over the period studied. There is concern for low morale within the Science Base. There is no statistical evidence of a brain drain, but concern about recruiting and retaining enough of the best young people remains.

14. Mr Baker, then SoS for E&S emphasised in his Academia Europaea speech (June 1989) that there should be clarification of the dual support system. This requires much better cost information. DES are consulting on shifting some money for overheads from the UFC to the Research Councils.

Handling

15. Sir Graham Hills, Chairman of the ACOST Study Group on the Science Base set up in July 1989, will introduce the paper.

Better levels of equipment
Research Council - provision for
cc. univ. provision

16. We know that the following would also like to contribute to the discussion:

* Professor Thomas Blundell
* Sir George Porter
* Sir David Phillips
Professor Roy Anderson
Professor Leonard Maunder
Professor Keith Peters
Professor Gareth Roberts
Professor John Robertson
Professor Christopher Llewellyn Smith

* members of the Science Base Study Group

17. OUTCOME - Agreement on recommendations for the final report.

Points for discussion

18. The report's recommendations need to more specifically address the two main issues which have been identified, first the need to have clear and complementary roles for the UFC and Research Councils. The dual support system does not clearly allocate funding responsibilities for teaching and research. It also encourages a marginal costing mentality.

19. The second is the need to ensure that emerging young researchers are properly supported. Points for discussion might be:

i. What improvement of the dual support system is needed?

ii. Support for the best young scientists - Does UFC money reach them? Should UFC money be earmarked for this?

ITEM 4: ADVANCED MANUFACTURING TECHNOLOGY 4.05-4.30 approx

Paper - AST(90) 8, Advanced Manufacturing Technology
+ synopsis at FLAG F

Background

20. The paper (AST(90) 8) has been prepared by a sub-group of the Emerging Technologies Committee on the application of Advanced Manufacturing Technology (AMT) within UK industry. It has been asked to consider whether there is need for a further initiative by Government to heighten awareness of AMT and to promote the wider dissemination of best practice.

AMT sub-group.

Handling

21. Professor Leonard Maunder, Chairman of the ACOST Committee on Emerging Technologies will introduce the paper.

22. We know that the following Members would also like to contribute to the discussion:

* Professor John Robertson
* Professor Keith Peters
* Dr David Smith
Professor Gareth Roberts
Mr Tony Gill
Mr Terry Harrison

* members of the Emerging Technologies Committee

23. OUTCOME - Guidance to the Emerging Technologies Committee on future work.

Points for Discussion

24. The report usefully analyses the present situation and the limitations of past initiatives. There is familiar emphasis on 'short-termism'. The principal issue, not addressed by the recommendations, is a lack of awareness and conviction by senior management at board level of the crucial importance of a disciplined and professional approach to manufacturing. Points for discussion might be:

i. Why did the previous initiatives in this area have such limited success?

ii. To what extent is the lack of commitment of top management to the introduction of AMT at the heart of the disappointing level of up-take?

iii. Is an enhancement of the present DTI awareness campaign likely to be effective in changing attitudes within Boardrooms?

iv. Until the commitment of top management has been obtained, would not a further initiative focusing of technical awareness, technology transfer etc be premature?

v. How do we go about obtaining the commitment of top management? Is it a job for Government or industry itself?

SIR JOHN FAIRCLOUGH
Chief Scientific Adviser

From: THE LORD FLOWERS, FRS
Chairman of the Select Committee on Science and Technology

Cc PS

COMMITTEE OFFICE
HOUSE OF LORDS
LONDON SW1A 0PW
01-219 3218/3346/6075

6 March 1990

My dear Prime Minister,

Scrap Part 9

CIVIL R&D

The Committee are grateful for your reply, dated 13 November 1989, to our report on Civil R&D.

There is a single point concerning ACOST which we would like to pursue. When we first recommended a body such as ACOST, we had in mind a triangular relationship between ACOST, the Government and the public. Your reply seems to favour a bilateral relationship between ACOST and the Government.

We do not dissent in any way from the proposition that ACOST should give some advice to the Government in confidence. But we suggest that ACOST will be most effective if it is also empowered to act as a catalyst to accelerate developments outside Government. For this purpose we proposed that ACOST make a biennial report to Parliament, assessing progress and priorities in science and technology, in an overtly strategic way. The Annual Review of Government funded R&D, valuable as it is, does not fit this bill.

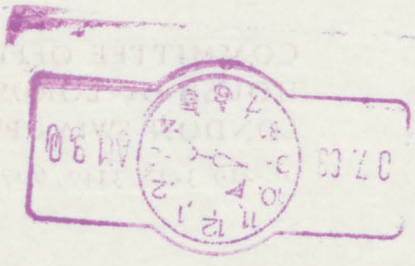
Do you not agree that the stimulus of ACOST's report could help industry, the academic world and Government to recognise their common interests and could by persuasion encourage them to pursue complementary objectives, in support of national wealth?

Would not regular reports to Parliament be an appropriate way to achieve this?

Yours ever
Brian
FLOWERS

The Rt Hon Margaret Thatcher MP

SCIENCE: Budget- Part-10



ATTENDANCE AT ACOST MEETING ON 14 MARCH, CHAIRED BY THE PRIME MINISTER

ACOST MEMBERS

Lord Tombs FEng	Chairman, Rolls-Royce plc
Prof Roy Anderson FRS	Dept of Pure & Applied Biology, Imperial College of Science
Prof Thomas Blundell FRS	Dept Crystallography, Birbeck College
Dr Peter Doyle	Director of Research and Technology, Imperial Chemical Industries plc
Mr Anthony Gill BSc FEng	Chairman, Lucas Industries plc
Mr Terry Harrison FEng, BSc, FIMechE, FIMarE	Chairman, Northern Engineering Industries plc
Mr Ian Harvey	Chief Executive, British Technology Group
Sir Graham Hills FRSC FRSE	Principal & Vice Chancellor, University of Strathclyde
Prof Leonard Maunder OBE FEng	Dept of Mechanical Engineering, University of Newcastle-upon-Tyne
Prof Sir David Phillips FRS	Chairman of the Advisory Board for the Research Councils
Prof Keith Peters FRCP	Regius Prof of Physic, Cambridge, University Clinical School
Sir George Porter PRS	President of the Royal Society
Prof Gareth Roberts FRS	Director of Research, Thorne EMI and Prof of Engineering Science, University of Oxford
Prof John Robertson	Dept Electrical Engineering, University of Edinburgh

Dr Alan Rudge OBE FEng FRSA	Director of Research and Technology, British Telecom plc
Sir Alfred Shepperd	Chairman, The Wellcome Foundation Ltd
Prof Christopher Llewellyn Smith FRS	Chairman of Physics, University of Oxford
Dr David Smith	Chairman of Physics, University of Oxford Consultant

INVITED SPEAKERS

Professor John Harper FRS	Emeritus Professor, School of Plant Biology, University of North Wales
Professor Harold Woolhouse	Director of Research, AFRC Institute of Plant Science Research

NO 10

Mr Guise

Mr Turnbull

CABINET OFFICE

Sir John Fairclough	Chief Scientific Adviser

ACOST SECRETARIAT

Dr Clive Bradley

Mr David Lobley

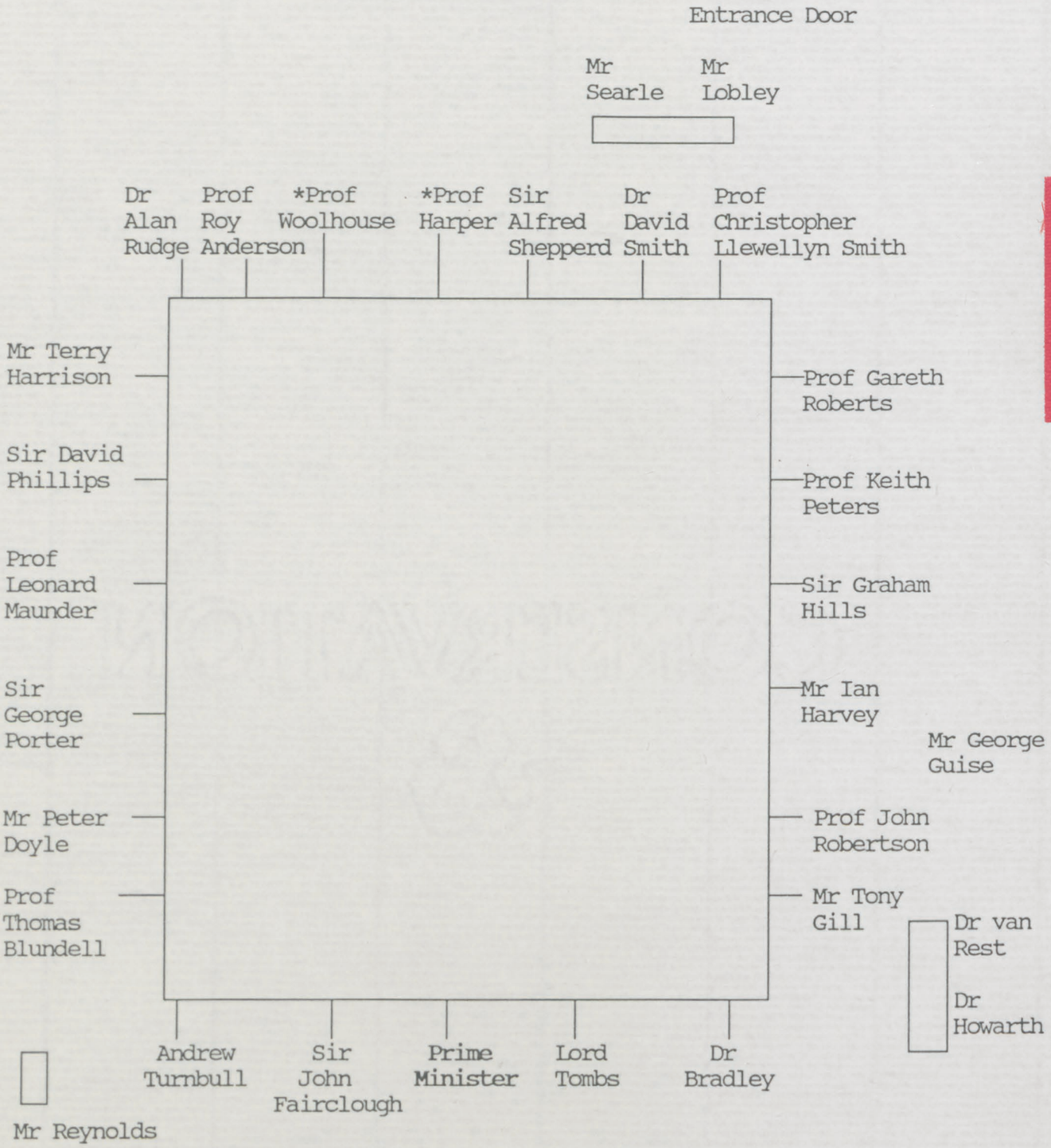
Mr John Reynolds

Dr Bill Maton Howarth

Dr David van Rest

Mr Callum Searle

TABLE PLAN FOR COMMITTEE ROOM A FOR THE MEETING WITH THE PRIME MINISTER ON WEDNESDAY 14 MARCH 1990



* for Agenda item 2 only

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AST(90)2nd Meeting
14 March 1990

COPY NO

ADVISORY COUNCIL ON SCIENCE AND TECHNOLOGY

Meeting to be held in Conference Room A
Cabinet Office, 70 Whitehall
on WEDNESDAY 14 MARCH 1990 AT ~~2.30~~ 3.00 pm

AGENDA

1. CHAIRMANS OPENING REMARKS

2. ADAPTIVE BIOLOGY
   Note by the Secretary
   AST(90)10 - already circulated

3. INTERIM REPORT OF THE SCIENCE BASE GROUP
   Chairman's cover Note
   AST(90)9 - already circulated
   AST(90)11 - to be circulated

4. ADVANCED MANUFACTURING TECHNOLOGY
   Note by the Secretaries
   AST(90)8 - already circulated

Signed
Dr C C BRADLEY
Mr J REYNOLDS
Dr D J van REST
Dr W M HOWARTH
Mr D H LOBLEY
Mr C R SEARLE

Cabinet Office
6 March 1990

Note: Members are asked to arrive no later than 2.45pm for the meeting.
Apologies and queries to the Registry : 01-270 0105

SYNOPSIS OF AST(90)10 AGENDA ITEM 2

ADAPTIVE BIOLOGY

1. Professor Harper's paper discusses natural adaptation and argues that existing organisms are a result of their history. Past adaptation fits organisms better for the future only if the future continues to be like the past. He then considers the direction that man has given to the evolutionary process through breeding and deliberate selection of crops and animals for present conditions.

Over the next 50 years the greenhouse effect could raise the mean temperature by 5°C, though there would be wide local variations. To meet this, natural organisms have two options - to migrate or to stay and adapt. Natural ecosystems may not be able to cope with such a rapid rise in temperature.

We need agricultural strategies and crops that can cope with variable environments. Internationally held gene banks will be of crucial importance as sources of genetic variation.

2. Professor Woolhouse's paper highlights the importance of understanding the mechanisms of adaptation at the molecular level, not only for underpinning options to counter any greenhouse impact, but also for improving and exploiting plants, animals and microorganisms for agricultural and industrial processes. He outlines the advances already made through the use of new techniques in molecular biology and molecular genetics and lists the following areas for further effort:

- study of bacteria for model systems
- study of regulating genes
- storage of genetic material
- study of adaptation of long-lived species eg trees
- supplementation of molecular studies with whole-organism studies under field conditions

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AST(90)10 COPY NO. 61

1 March 1990

ADVISORY COUNCIL ON SCIENCE AND TECHNOLOGY

ADAPTIVE BIOLOGY

Note by the Secretary

1. Council commissioned two papers on Adaptive Biology from Professor John L Harper FRS, University of North Wales and Professor Harold Woolhouse of the John Innes Institute. The authors have considered environmental issues in their papers.

2. Professor Harper's paper (Annexe A) introduces the question of natural adaptation and how this is the result of history and so does not necessarily fit organisms better for the future. He also considers the question of shorter timescale changes in response to external influences, including human intervention in the evolutionary process. He then examines the likely responses of organisms to changing climate, including the adaptation and migration of species and the consequences of this on agricultural practices.

3. Professor Woolhouse's paper (Annexe B) considers the recent advances in molecular biology, which have created important new opportunities for the study of adaptation. He outlines how man's intervention has reduced genetic variability and stresses the need to maintain genetic diversity for the future.

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4. These two papers were considered at the first meeting of the ACOST Standing Environment Committee on 26 February. The discussion highlighted the following issues:

i. Gene Banks - the potential environmental changes will make international gene banks a vital source of genetic variation. These have traditionally been collections of seeds, semen or ova. However, new techniques are making it possible to store the genome of organisms in a cloned state in test tubes. This means that vast numbers of genes from many species and individuals, some of which may be extinct or long deceased, can be stored indefinitely for future use.

ii. Temperature Response - plant distribution is generally influenced by mean temperature rather than, as may be expected, extremes. It is difficult for plants to adapt to temperature changes so it is likely that species will migrate in response to the greenhouse effect. In the UK, agriculture should be able to adjust quickly but conventional conservation may prove impractical. The range of possible climates for the UK already exists in Europe, providing the opportunity for research and comparison.

iii. CO2 Concentration - some preliminary trials in small scale chambers on the effects of increased CO_2 concentration on plants have been recently initiated. The authors argue that there is also a need for large scale experiments on the long term effects on crops and other ecosystems. These could be undertaken by piping scrubbed CO_2 from the chimneys of power stations to open sites and semi open chambers containing defined ecosystems. In these the effects of CO_2 on adaptation could be assessed.

iv. Molecular Biology - the technology now exists to enable the direct manipulation of the genome of an organism which contains the DNA which constitutes the genetic code of life. The developing databases are making it possible to follow in precise detail the evolutionary changes in the lineages of specific genes. This provides a fresh insight into the process of evolution and of adaptation to environmental factors. At present it is not possible to infer how the change in a particular gene alters the fitness of the whole organism. This will require genetic manipulation combined with study of the fitness of the manipulated organism in natural and managed environments.

5. The authors will attend the meeting and give a short presentation on their papers. Council may wish to consider points (i to iv above) in the discussion and give guidance to the Environment Committee on the areas for further consideration.

Signed J REYNOLDS

Cabinet Office
1 March 1990

Annex A

Paper by, Professor John L Harper FRS,

University of North Wales

ADAPTIVE BIOLOGY

Types of 'Adaptation'.

The characteristics of organisms have changed through their natural evolutionary history, and also as a result of controlled breeding by man. Moreover the behaviour of an individual organism may change during a single life-time when it is exposed to changing environmental conditions. All of these changes may be loosely described as 'adaptation'.

(i) The natural evolution of ad-(ab-)aptations

The long neck of the giraffe makes it able to browse on tree foliage that is not available to other grazing animals. Ancestral forms with slightly longer necks presumably had better access to high foliage than their shorter necked brethren. They therefore grew faster or survived longer and left more descendants. Because neck length is heritable, successive generations developed (on average) longer necks. The long neck is said to be an adaptation. We have to be careful that we do not interpret this evolution as in every respect 'a good thing' for giraffes. There are costs, for example the long neck makes it extremely difficult to graze low growing herbage and the 'adaptation' whiIe allowing the giraffe to do one thing rather well constrains it from doing others. Similarly the gills and fins of fishes may be seen as adaptations to life in water, but at the same time they forbid life on land. Probably every evolved adaptation' brings some costs as well as benefits.

"Adaptation' in this evolutionary sense is a property that comes about because some variant organisms leave more descendants than others, and some of the variation is heritable. The result has been the evolution of a great variety of types of organism, each more or less specialised (adapted) to a different life style, able to do some things but constrained from doing others.

It is a common error to think that the evolution of adaptations necessarily fits organisms better for the future. The process is historical, ruled by which types of ancestor left most descendants in the past. What we see now is the result of history, not some anticipation of the future. The natural evolution of adaptations fits organisms better for the future only if the future continues to be like the past. The word 'adaptation' unfortunately carries the dative implication that the evolutionary process is to or for the future. Some of us now prefer the word abaptation which more clearly implies that it is by or from the past.

(ii) Adaptation of plants and livestock by man

When man intervenes in the evolutionary process he gives chosen direction to the evolutionary process. In breeding programmes he determines which individuals contribute most descendants (or genes) to future generations. The 'adaptations' that he aims to develop in organisms (e.g. fan tailed pigeons or short strawed wheat) are fundamentally different from those in (i) because man imposes a goal on the evolutionary process the 'adaptive' changes are planned for some future role (e.g. a new environment or market). The process of adaptation is then governed by anticipation of the future not by the consequences of the past. Adaptation by the hand of man has resulted in types of organism as bizarre as those produced in nature (e.g. turkeys 'adapted' to produce

thick breast flesh but which cannot mate naturally and require artificial insemination). But biological adaptation in the hands of man has depended on the same fundamental process as natural evolution - i.e. some of the variation in organisms is heritable and some organisms (or genes) leave more descendants than others. The major change in the process that has occurred through modern technologies of genetic engineering is that it has become possible to move the heritable properties (genes) from one potential ancestor to another without the slow (and sometimes impossible) processes of sexual reproduction.

The 'adaptation' of organisms for some planned role in the future depends, quite unlike natural evolution, on efficient prediction. For example it may be predicted that a variety of wheat resistant to a mildew will give a higher yield than present forms. The plant breeder may then control and direct evolutionary processes to 'adapt' the cereal to resist attack by the mildew. The process is not unlike that of choosing a new portfolio of shares determined by how it is anticipated it will perform in the markets - natural evolution, in contrast, is more like an inheritance of a portfolio of which some parts had performed well in the past.

A single tree may develop different forms of leaf on branches that are in the sun and the shade. A bear may develop a thicker coat on the approach of winter. The ability of an organism to make such 'tactical' responses is of course one part of its evolutionary inheritance - the ability of some ancestors to make more tactical changes than others will have influenced which left most descendants.

We can recognise two types of 'adaptive' response that an organism may make during its life. (a) It may react to its present experience. A rose will come into leaf early and a hedgehog will break its winter dormancy if the winter is

unusually mild. Such behaviour may bring rewards if the remainder of the season remains warm. The early growth response might then prove 'adaptive', 'a good thing'. However a late spring frost would kill or damage the foliage and the rose then depends on a (costly) act of replacing its foliage- the hedgehog suffers by awakening when food is scarce. (b) It may react to some cue to an approaching experience, rather than to the experience itself. The most common cue is the seasonal change in day length. The breeding seasons of many animals and plants are timed by information about day length and the possession of biological clocks. Cues allow organisms to adapt by anticipating seasonal change (e.g. as days shorten the bear starts to put on a thick winter coat that anticipates the oncoming winter). Of course the organism does not itself anticipate the seasons; rather, ancestors that had such a clocking mechanism presumably left more descendants than those that lacked it. Cued adaptations guard an organism against inappropriate behaviour in the odd unusual seasons e.g. waking up or growing too soon in an unusually warm winter.

The adaptive responses of an organism to its immediate environmental experience may be thought of as tactical and opportunist, bringing occasional high rewards but high risk. Adaptive responses that depend on cues (such as biological clocks) are in a sense strategic and reduce risks but sometimes miss opportunities. Despite old wives' tales there is no evidence that there are biological cues that predict especially hard winters or droughty summers. The truly reliable and predictable changes in the natural environment are seasonal (that summer usually follows spring), diurnal (that night usually follows day), and regional (that the environment of Manchester this year is likely to be much the same next year (at least more similar than the environment of Exeter or Madrid).

This set of general statements about the various processes that biologists regard as 'adaptation' can be used as a background against which to consider how populations of organisms in nature are likely to respond to major environmental changes such as the greenhouse effect and how man might appropriately change his domesticated plants and animals to fit them for changed environments or markets.

Biological adaptation to changing climates.

Predicted greenhouse effects pose obvious questions about biological adaptation. The firmest predictions are that atmospheric CO_2 concentrations will continue to rise and mean temperatures increase by ca. $5^{o}C$ over the next 50 years. It is unfortunately much more difficult to predict changes in the rainfall pattern - droughts might become much more or much less frequent. It seems likely that climatic variance will increase and that prediction from year to year and perhaps even from week to week will become more difficult.

Environmental uncertainty does not make it impossible to predict biological response. Much of evolutionary theory has been concerned specifically with adaptations to life in naturally unpredictable environments. For example, desert and monsoon environments contain many species with life styles that have flourished despite chaotic year to year variations in rainfall. I consider first the responses that may be considered adaptive in environments in which the direction of change is reasonably predictive.

(i) Adaptation to predictable environmental change

There are two simple responses of organisms that can result from a change in the environment. Their characteristics may remain unchanged but they migrate elsewhere, or they adapt to the changed circumstances and stay where they are. The two

responses may be mixed in different proportions. During climatic cycles of the ice ages there were probably some genetic changes among species, but in general the species responded by changing their distribution. In natural communities this is unlikely to be an easy response to the greenhouse effect partly because the speed of predicted change is so much faster than that in interglacial episodes, partly because natural vegetation no longer forms a continuum but is broken by agriculture and human communities into a patchwork: migrations must now occur across large gaps and be much more risky. The greenhouse effect may indeed make conventional nature conservation impracticable and need deliberately assisted migration of species to deliberately created new reserves. The situation for agriculture is much simpler. In the short term, farming practices will probably migrate in order to stay in their customary climates, rather than that the crops and livestock species will be adapted and remain where they are at present.

Most of the sorts of environments that are realistic scenarios in the U.K. in the next 50-100 years already exist elsewhere on the continent of Europe. As the greenhouse effect forces types of agriculture to migrate across Europe a few crops will require some 'adaptive' adjustments to their biological clocks: this is probably relatively easy for the breeder of short lived crops (trees pose a special problem because those we plant now will mature in a quite different climate). It is probably not too difficult to predict the patterns of crop production in the U.K. and the continent that would result from a 5°C rise in temperature though we would need to have scenarios that included maintained, increased or decreased rainfall.

Depending on the speed of climatic change and the conservatism of agricultural practices there may be some pressure to continue growing crops and livestock in the same places and to adapt them to the changed local conditions. It should not be difficult to design traditional breeding and bioengineering programmes to adapt organisms to life at higher temperatures (and higher CO^2 concentrations). Much effort has been aimed in the opposite direction - breeding for tolerance of lower temperatures, (e.g. the breeding of maize suitable for cooler regions and shorter growing seasons). Between 1920-30 and 1940-49 maize production in Iowa and Illinois increased by 21.6% and 27.3% respectively but in the more northern state of Wisconsin increased by 54.3% and in 1953 the average grain yield of maize exceeded that of any other state for the first time in history.

In a changing environment the breeder needs access to heritable variation that is relevant to the new environmental conditions. It is hard to overestimate the importance of internationally held gene banks which can be used as a source of genetic variation for adaptive genetic change.

(ii) Planned 'adaptation' of animals and plants to unpredictable environments

If some aspect of the environment next year, or 50 years ahead is likely to change but the direction is uncertain (e.g. the rainfall in the U.K. as a result of the greenhouse effect) it is obviously impossible to make a single blueprint that will always represent an organism's optimal biology. The analogies with designing a stockmarket portfolio market are very obvious and so are the compromise solutions.

(a) There are forms of plant and animal that maintain rather constant performance in volatile environments (gilt edged adaptations!). A study of the

yield of barley varieties over climatically ver[illegible] different years and soil conditions identified strains that had remarkably stable (though never particularly high) yields. The property (homoeostasis) can clearly be fixed in at least some organisms and is one strategic response that might be adopted by breeders in 'adapting' crops or livestock to uncertain future environments.

(b) A contrasting 'adaptation' to uncertain environments is greatly to exploit the occasional favourable season, even though performance at other times may be very poor. There are many organisms in nature that have this behaviour even, like many weeds, remaining dormant during unfavourable seasons or years. This opportunistic adaptation to unpredictable environments is one feasible 'adaptation' in agricultural practice, providing the glut from past years can be stored for use in lean years, (possible for grain but not for potatoes, possible where there is efficient storage but not where pests of stored products are a problem). It is clearly a possible adaptive strategy for cropping in an unpredictable environment (indeed grain mountains might be seen as an aspect of this strategy). As an adaptation to food production in an unpredictable environment it is inevitably costly; in the investment analogy, capital lies idle or wasting during many years though the long term gains may still be real.

(c) Bet Hedging.

If the individuals in a population differ from each other, there may be less chance that they all suffer from the same disaster. There is a mass of evidence

that genetic diversity is often favoured in natural environments. In successive years some individuals (or different patches within an environment) produce a disproportionate amount of seed or progeny but in another year it will be individuals with a different genetic constitution that are most productive. Over the years the populations with the greater diversity produce the most reliable yields (in any one year one variant will usually have performed best but which one is known only with hindsight). This is of course essentially the analogue of the broad spread strategy of financial investment.

The exploitation of the bet-hedging strategy in agricultural practice is at its most obvious in mixed farming systems. There are however good examples of the use of diversity within populations of crop species as a guard against unpredictable events. An important unpredictability in cereal production is the occurrence of strains of disease organisms (e.g. mildews and rusts) which are specialists on particular cereal varieties. If it were known in advance which strain of the disease was going to develop it would be possible to sow the appropriate resistant variety of the cereal but prediction is extremely difficult. A solution is to sow a mixture of varieties. In any year only a proportion of the crop suffers. The risk of spread of the disease among susceptible plants is further reduced because they are interspersed with resistant forms. Moreover, the plants in the mixture which suffer from the disease leave more resources of light, water and nutrients for those that are resistant. The spreading of a risk by the deliberate use of controlled diversity in crops (and perhaps also livestock) may be an important way in which 'adaptation' of biological

systems to unstable or unpredictable environments may be achieved. This has certainly been a feature commonly selected for by unpredictable environments in nature.

In any consideration of the 'adaption' of organism to environmental change we can draw on a well developed body of evolutionary research, much detailed knowledge of the responses of natural vegetation to climatic change in interglacial periods and much experience of plants and animal breeding. But the predicted pace of change in the greenhouse effect is extremely fast. Other things being equal, a difference in mean temperature of 1^{oC} corresponds with a 100km movement of forest margins. A rise of 5^{oC} gives a world hotter than it has been since before the evolution of Homosapiens. The speed of genetic change in natural evolution and in conventional breeding programmes depends on the lengths of life cycles. Genetic engineering may be able to speed up the process. It is the predicted pace of the change and increasing variance of climate in the greenhouse effect rather than change in itself that set the real problems in biological and cultural adaptation.

Annex B

THE STUDY OF ADAPTATION IN THE ERA OF MOLECULAR BIOLOGY

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Contents

1. SUMMARY AND RECOMMENDATIONS

I deal briefly with the following matters:-

i. Adaptation is a vast subject that is central to much of biology. Understanding the mechanisms of adaptation is of strategic importance for the improvement of plants, animals and microorganisms for agricultural and other industrial purposes.

ii. From the beginning of this century, adaptation has been extensively studied by biochemists, population biologists and population geneticists, following the flood of work by comparative anatomists and physiologists which came in the wake of Darwin's theory.

iii. Starting in the nineteen sixties, the introduction of the techniques of molecular biology and molecular genetics into the study of adaptation has changed our perception of the subject. Previously unsuspected molecular mechanisms underlying adaptive changes have been discovered and the development of a unified view of the interrelationships between environmental factors, molecular processes and phenotypic responses has become a possibility.

I make the following recommendations:-

i. Bacteria are very convenient model systems for the study of adaptation; there has been some decline in support for work with microorganisms in recent years, this is unwise.

ii. Regulatory genes will be of crucial importance for a proper understanding of adaptation; we should increase our research effort in this area very substantially.

iii. The ability to isolate, clone, sequence and store indefinitely vast numbers of genes from many species and individuals, some of which are extinct or long deceased opens a completely new horizon for the preservation of biological variation on the earth. We need new international approaches to systematic collaboration in this field.

iv. For reasons of experimental convenience and short term economic advantage there is great current emphasis on the genetic manipulation of short-lived food plants, which are often poorly adapted. Strategically it is probably far more important that we should become concerned with the molecular biology of adaptation in trees and other long-lived species.

v. I have explained <u>why</u> it is important to recognise that work at the molecular level supplements studies of whole organisms under field conditions and does not supplant them. Translating this into current concerns over climatic change I make a specific case for large scale experiments on long term effects of elevated CO_2 concentrations on crops and other ecosystems.

vi. The molecular biology of adaptation is a study which is in its infancy, but the framework of enquiry in now sufficiently defined to warrant greatly increased investment. Along with the study of development I would rate adaptation as one of the most important areas of biology in the years ahead.

2. <u>What is adaptation: defining the problem</u>

"Adaptation is a special and onerous concept that should be used only where it is really necessary" Williams, G. C. (1966).

We live in times when there are indications that the population explosion of Homo sapiens may lead to increased rates of change in critical features of the climate and the gas composition of the atmosphere of the earth. The study of these changes is in its infancy. There is as yet insufficient evidence to indicate just how rapid or how great these changes may be, although the increasing carbon dioxide concentration in the atmosphere is now being charted with considerable accuracy. We can confidently assert that this factor alone will have profound effects on the patterns of vegetation and the productivity of plants. It becomes important to know about the capacities of organisms to adapt to these increases of CO_2 and the changes in climate which may follow. A crucial question here of course is the rates of change. The climate changes could occur on a timescale of decades. Some adaptive changes in the populations of some species might occur on a similar timescale but others could require hundreds or thousands of years or even longer. Almost certainly some of the mass extinctions seen in the fossil record have occurred when rates of environmental change have exceeded the rates of essential adaptive change in the contemporary populations. There then arises the interesting question of whether it might be possible to manipulate adaptive changes using genetic engineering techniques, but the great gap in our current understanding between phenomena at the molecular and organismal levels makes this an unlikely prospect in the foreseeable future.

Since life developed on earth the better adapted organisms have been selected to meet the changing conditions. Adaptations are those attributes of organisms which, because they enhance their fitness, have been moulded by specific elements of natural selection acting on genetic variation. The success of a species of living organism may be measured in terms of its current abundance or the extent of its geographical distribution but these features of its

contemporary population structure are potentially transient and may have little bearing on its ability to survive over longer periods of time.

In branches of biology such as physiology and ecology the word adaptation used to refer to an individual organism's phenotypic adjustment to its environment, as in physiological acclimation. We are not concerned with these phenomena for present purposes.

Most studies of adaptation up to the nineteen sixties described the comparative anatomy, physiology and biochemistry of different species and interpreted the findings in relation to the environments in which the organisms occurred. Obviously, if one is considering the locomotion of migratory birds high in the jetstream or of fishes kilometres down in the deep ocean, then ones interpretation of what is found will only "make sense" when considered in relation to the physical conditions in the two media. Similarly, an understanding of form and functioning of plants from such different habitats as deserts, bogs and salt marshes requires knowledge of the physical and chemical characteristics of these habitats. The general principle underlying investigations into the design and functioning of organisms in relation to their environment is the supposition that the environment appears to a population of organisms as a set of problems to which it responds over a period of time by making genetic changes. These changes can be interpreted as "improvements" if they benefit the working of the organisms and hence ultimately the fitness of the population. In the language of the theory of evolution the organisms are involved in a struggle for survival in the face of the combined challenges of their physical environment and of competing organisms. Collectively, the organisms in a population possess variation, which they can pass to their offspring thereby helping them in their struggle by providing adaptations.

3. Adaptation in the context of agriculture and forestry

It is important to recognise that in agriculture most species are not adapted in the course of evolution, rather they are manipulated by man. One consequence of this is that in most cases agricultural crops tend to have a much reduced genetic variability when compared with related species in natural plant communities. It is for this reason that most agricultural crops have to be sustained by elaborate and expensive inputs of irrigation water, fertilisers and protective chemicals which are expensive for the farmer and of increasing concern to the water authorities and environmentalists. Genetic engineering offers some possibilities for restoring genetic variability to our crops, but as I explain in Section 6 it would be naive to suppose that in any but a few relatively trivial caseses do we have a sufficient knowledge of the molecular basis of adaptive processes to make this a reality at the present time.

It is also important to note that long-lived organisms and in particular trees do not turn over their generations quickly enough to make the adaptive changes that may be necessary to match environmental changes. With this in mind the current relative neglect of tree biology is particularly unfortunate; as tissue culture techniques make it possible to shorten generation times for trees there is need for a very substantial increase of effort in this area.

4. Molecular Biology in the study of adaptation

The first impact of molecular biology on the study of adaptation came in the mid 1960's when the technique of gel electrophoresis for the separation of proteins made it possible to survey protein variation across large numbers of individuals and species. It was found that most populations of higher organisms were highly variable. For some enzyme proteins, identifiable by specific staining of their reaction

products, there were ten or more variants of the enzyme to be found in a given population. This enzyme variation or polymorphism might be seen as the variation on which the forces of selection could operate, but if this is the case it poses a problem. Thus, if many individuals in a population are carrying functionally significant variants of some components they cannot all, by definition, be optimally fit: so the argument runs that there must be a cost to the carrying of the sub-optimal variation. This sub-optimal variation is often referred to as the genetic load. If the load is too great the population will be so far from optimal fitness that it will die out. A way out of this difficulty was to suppose that most of these protein polymorphisms were making no difference to the fitness of the organisms, that is to say they were not affecting its adaptation and were selectively neutral.

Over the past twenty years a mass of evidence has been accumulated some appearing to favour a dominant role for selection, some in favour of neutral changes.

Fortunately the techniques of molecular biology have moved on so that we can handle directly the DNA of which the genes are made and study their coding sequences. As the techniques for sequencing genes are streamlined and automated there is developing a vast database in which it becomes possible to follow in precise detail the evolutionary changes in the lineages of specific genes. Some biologists have been inclined to dismiss these developments as a misguided reductionist enterprise which will contribute nothing to our understanding of adaptation at the phenotypic level. As recent developments make abundantly clear the contrary is true: new knowledge of molecular details provides completely fresh insights into the processes of adaptation. We should now consider some current developments which illustrate this view.

5. Generation of variation at the molecular level

The availability of rapid DNA sequencing techniques makes it possible to determine a lot of gene sequences and compare sequence lineages from groups of species whose divergence from a common ancestor is dateable from the fossil record. From this we can work out the rates of change of particular genes over long periods. This capacity to isolate, sequence and store genes have some very interesting implications. First, it becomes possible to isolate and clone genes from very tiny pieces of ancient tissue, for example frozen or dried fragments from such extinct species, as mammoths and giant sloths or of mummified human remains from archaeological sites.

Second, it should become possible to see something of the changes which took place in particular genes in periods of rapid environmental and climatic change in times past.

Third, it becomes possible to develop real gene banks, that is collections of cloned genes stored individually in a stable condition in test tubes. We tend to use the term gene bank at the moment for collections of seeds, semen or ova and these have great importance in preserving particular organisms against extinction or loss of variation. However, the capacity to isolate and clone thousands of variants of particular genes from almost any organism and to store them cheaply and easily offers a most important new tool for preserving and reintroducing genetic variation which might otherwise be lost. Thus for example, it will become possible to clone and preserve the whole of the DNA of the chromosomes of many flowering plants and animals in as few as 100 to 1000 samples. From these stored samples the DNA can be withdrawn, sub-cloned and used to reintroduce into a living organism at any time in the future.

Studies in plants of unstable genes, that is genes with exceptionally high mutation rates, led to the discovery of mobile pieces of DNA which have come to be known as transposable elements. Transposable elements can move around the chromosomes creating mutations as they insert and excise from the genes, which has led to the suggestion that their biological function is to help generate genetic variation. Transposable elements have been found in all groups of organisms in which they have been sought, but the detailed analysis needed to reveal their biological significance has only proved possible to date in a few specific cases in bacteria, yeasts and fruit flies.

Further support for the importance of mutations as a source of adaptive variation comes from the finding of the so called SOS responses in bacteria which are elicited by environmental stresses. SOS responses include increased rates of several types of mutation, and enhanced capacity for DNA repair. There is preliminary evidence that similar responses may occur in animals and plants.

6. Some constraints on adaptive processes

Not all changes which might improve the fitness of a population are feasible in terms of the variation that it has acquired in the course of its past history. Plants provide an example of what appears to be a significant adaptive constraint at the biochemical level. The enzyme which fixes carbon dioxide in photosynthesis has two defects, it is unable to discriminate completely between the desired substrate, CO_2, and molecular oxygen and it has a relatively low affinity for CO_2. The competitive reaction with oxygen leads to a wasteful sequence of reactions whereby carbon is lost again in a process known as photorespiration; whilst the low affinity for the substrate means that the plant has to invest some fifty percent of the soluble protein in its

leaves in making large quantities of the enzyme. At least a billion years of evolution appear to have failed to overcome these dual constraints affecting the substrate supply for carbon dioxide fixation, leading to the suggestion that this may reflect an intrinsic design constraint.

Constraints to change are also found in the genetic material, for example some bases are found to mutate more frequently than other bases, while chromosomes are well known to have 'hot spots' which break and mutate more readily than other regions.

Another class of constraint upon the types of adaptive responses which an organism may adopt arises from the hierarchical nature of the levels of organisation in the organism. I can best explain this by recourse to a diagram (Fig 1). If the argument here becomes a little technical, I crave the readers indulgence on the grounds that this matter of the hierarchical nature of organisation is of crucial importance if we are to avoid drawing simplistic conclusions of a popularist kind which gives the impression that the problems of biology are nearing solutions.

Figure 1 shows four levels of organisation, the regulatory genes (Gr), the genes encoding enzyme in proteins (Gp), the proteins (P) and their biochemical products comprising the cells and the phenotype. Figure 1 shows a more elaborate version of the network of interactions between processes at these different levels of organisation. The important point to note is that we have no simple or readily predictable correspondence between specific gene mutations and their phenotype manifestations. Some idea of the magnitude of the task in unravelling such interactions may be gained from the fact that some recent estimates put the average number of metabolic reactions per cell at 500, involving up to 10,000 proteins with multiple feedback and reinforcement at various levels.

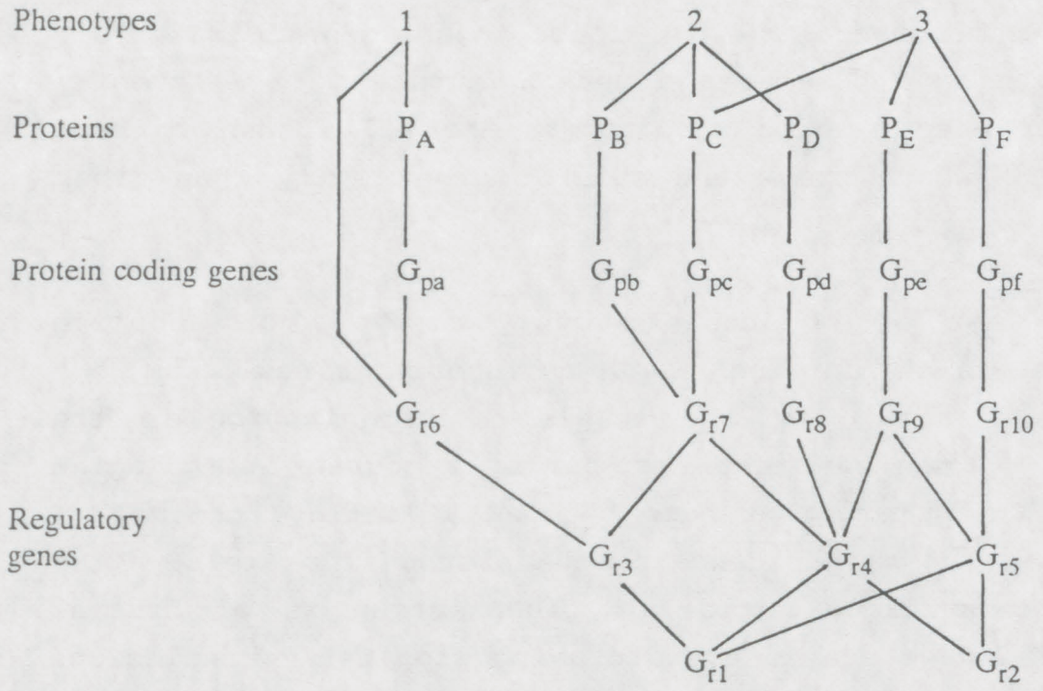

Figure 1. Representation of the heirarchical structure of the eukaryotic genome.

There are two particular aspects of this situation which call for special comment, these concern the identification of the regulatory genes shown in the diagram, that is genes operating deep in the central network of the organism which serve to control the expression of other genes rather than encoding for specific enzyme proteins, and the scope for studying the interrelationships of parts of the network by altering the "wiring", that is to say the various interactions on the feedback loops. These are important and expanding areas of research which warrant increased support. Until recently it was possible to postulate the existence of regulatory genes from genetic analysis, but lack of any knowledge of their products and the fact that they are needed in only trace amounts presented formidable obstacles to their isolation. Recent technical developments have led to the isolation of regulatory genes by gene cloning. This has led to progress in understanding such processes as regulation of cell division, control segmentation in insects and the development of floral parts in plants. These basic control mechanisms play a key role in many aspects of adaptation. Having isolated specific regulatory genes, one can mutate them *in vitro* and then reintroduce them into the organism from which they originated and hence explore the consequences for development, performance and adaptive fitness. This may be regarded at first as an over-optimistic programme but such manipulations can now be done readily in microorganisms which makes them very important as model systems. Moreover, recent work involving the genes affecting rhythmic behaviour patterns in the fruit fly *Drosophila* have demonstrated the feasibility of this approach in eukaryotes.

I should emphasise that this is one of the most important and exciting areas of modern biology, it is one in which we have a very substantial stake in this country, and one in which we should increase substantially our level of investment.

7. Concerning rates of adaptive change

The fitness of a population of organisms will depend not only on its capacity for adaptive change, but also upon the rate at which it is able to adapt.

The role of sex and the modification of mating systems is one of the most intensively studied factors affecting rates of adaptive change. The major influence of mating system on the rate of adaptation arises because mating allows recombination which brings together potentially favourable variants from different sources.

Plants adapted to unstable habitats such as semi-deserts with sparse and erratic rainfall, often exhibit genetic polymorphism for features such as heterostyly and pollen-stigma interactions which produce varying degrees of outcrossing and self pollination. Self pollination frees the plant from dependence on a pollinator and can hasten the evolution of a reduced investment in aspects of floral design required to attract and nurture the pollinator. The first isolation of genes controlling the pollen-stigma interactions has recently been reported. Manipulation of these genes into other plants should make it possible to explore the consequences for the adaptive properties of the species as well as offering interesting possibilities for controlling of mating behaviour in commercially important plant varieties.

Phenotypic plasticity, is the ability of an individual to alter its physiology and morphology in response to changes in environmental conditions. Many successful weeds originated in unstable habitats. In these habitats they adapted by developing the capacity to regulate their allocation of resources so as to optimise their reproductive potential in relation to the current constraints of the environment.

One might suppose that if a species is able to tune its fitness by means of a high degree of plastic responses there would be no pressure for a genetic change in the characters per se. However, the few attempts that have been made to address this question have provided no evidence for differences in the rates of change of plastic and non plastic characters.

8. Concerning the direction and prediction of adaptive change

Reference was made earlier to the existence of SOS responses by which bacteria and possible higher organisms are able to increase their mutation rates under environmental stress. I should briefly mention here that some bacterial geneticists claim to have shown that particular environmental factors can initiate mutations which are specifically adaptive to those factors. These results have been interpreted in the popular press as evidence of purposive behaviour existing even at the molecular level. Careful reading of the literature forces one to the conclusion that there is as yet no clear evidence that such mechanisms exist and I propose to venture no further into this particular minefield.

The multitude of symbiotic relationships which exist between different organisms, as for example Rhizobium and plant roots, algae and fungi in lichens and bacteria in ruminants, provide adaptations which enable the partners to penetrate habitats where neither could have survived for long alone. In only a few cases, as for example Rhizobium legume interactions, have we scratched the surface of how these interactions are regulated at the molecular level, though clearly each partner must be influencing the direction of evolution and adaptation of the other.

In the preceding section I sought to emphasise that because of the hierarchical complexity of organisms, even with relatively simple bacteria we could not predict the consequences for the behaviour of the organism from the study of molecular changes alone. This issue becomes of great importance when we wish to know the directions of adaptive change which may follow from environmental changes. It is for this reason that in recent papers I have emphasised the importance of direct experimentation on the long term responses of crops and perennial vegetation to increased CO_2 concentrations. Recent work has made it possible to scrub both SO_2 and oxides of nitrogen from the chimneys of power stations; such a scrubbed source of cheap CO_2 could be piped to open sites and semi open chambers containing synthetic ecosystems so that effects of CO_2 could be studied on crops, woody species and plants in which attempts are made to genetically engineer adaptive responses.

9. Conclusion

I have endeavoured to show that the intrusion of molecular biology into the study of adaptation has opened up an array of new avenues towards the understanding of this vast and complicated subject. The intrinsic scientific interest of adaptation is sufficient alone to ensure it a central position in biological research but in view of what many would regard as the impending environmental changes, we should probably be well advised to invest more effort in this direction for practical purposes as well.

Harold W. Woolhouse
19.2.90

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SYNOPSIS OF AST(90)11 AGENDA ITEM 3

REVISED INTERIM REPORT OF THE SCIENCE BASE GROUP

1. Worries have been about underfunding and the changes in the nature and organisation of science. The Science Base has received increased funding in real terms over the last 10 years. But funding has decreased both as a percentage of GDP and in comparison with the spend of our major competitors. There is a decline in the UK share of Nobel prizes, patents, citation indices, peer reviewed papers.

2. Most funding for the Science Base comes from Government. University research income from industry and charities is increasing strongly. UFC funding increased slowly both in GDP deflator and UPPI (Universities Pay and Prices Indicator) terms until 1986/7 but has since fallen back in UPPI terms. University charge-out rates normally assume that overheads are fully covered by UFC funding. The success of universities in attracting underpriced grants/contracts can overstretch the UFC provision. Provision for equipment, overheads and technical staff have suffered.

3. The report refers to core science funding, unfunded alpha projects, academic salaries, migration, short-term appointments, equipment costs, size of research grants and the appropriate balance between directed and responsive mode Research Council funding. Significant points are: a measure of unfunded alpha grants may be healthy; academic salaries have kept pace with inflation but not with other employment categories; there is no evidence of a braindrain; there is concern that there are fewer small grants, with a growing share of funds for research by groups at the expense of the outstanding individual.

4. Science Base resources have held up reasonably well, alternative sources of income have been developed and considerable changes in the character and organisation of science have been carried through. There is little financial headroom and legacies of expectation from earlier periods cannot now be met.

SYNOPSIS OF AST(90) 8 AGENDA ITEM 4

ADVANCED MANUFACTURING TECHNOLOGY

Since the 1960s growth in manufacturing output has averaged less than 2% per annum. The annual rate of growth has increased to 3.8% since 1982, but this has still left the UK's value added per head significantly below that of our major competitors. The UK share of manufactured exports has fallen in contrast to our main EC partners.

2. Application of advanced manufacturing technology (AMT) offers major opportunities for higher productivity, efficiency and quality. It will be effective only if it is introduced as a fully integrated part of a company's strategy. Effective introduction depends on the company's top management.

3. Some UK companies have successfully taken an integrated approach to AMT. The majority of them are foreign-owned and have achieved it by inwards technology transfer.

4. A 1983 ACARD Report (New Opportunities in Manufacturing: The Management of Technology) called for Government assistance in promoting awareness of the advantages of AMT. A number of Government initiatives have been taken as a result. Private industry has also funded initiatives in specific areas of manufacturing technology. But they have not led to either wide-spread up-take of AMT or an integrated approach to its introduction.

5. The Report recommends that further consideration should be given to a new initiative by Government and that there should be renewed effort by DTI, the higher education sector and the business schools to enhance awareness and training in the AMT area.

6. Three options are outlined for a new initiative:

i. formation of a small coordinating group to act as a link between those already involved in various aspects of AMT.

It would act as a clearing house on the dissemination of best practice and might be given responsibility for funding or routing funding on R&D and technology transfer to other bodies.

ii. creation of a national centre for AMT.

iii. the Sub-Group favours a phased approach which starts with i. and moves to ii.

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SCIENCE BASE STUDY GROUP

REVISED INTERIM REPORT OF THE SCIENCE BASE GROUP

Note by the Secretaries

Minor drafting amendments have been made to the report. For completeness, a copy of the final version for use at the Council Meeting on 14 March is attached.

SIGNED C C Bradley
D J van Rest

Cabinet Office

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AST(90)9
5 March 1990

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ADVISORY COUNCIL ON SCIENCE AND TECHNOLOGY

SCIENCE BASE STUDY GROUP

INTERIM REPORT OF THE SCIENCE BASE GROUP

Chairman's Cover Note

This is an interim report on the the Science Base in the UK. The final report will be completed later this year.

This country's capability in the fields of science and technology is of great importance, reflecting as it does our attitute to this area of knowledge and expertise. It is also the intellectual foundation of our capacity to stay at the leading edge of manufacture and to play our part in the creation of new technologies. Britain has a good reputation in science and it should be maintained.

The health of Britain's Science Base is a matter of considerable public debate. There are those who argue that it has become increasingly underfunded for what it might be

expected to do. There is in this lobby a lack of understanding of the inevitable limits to unconstrained growth, even in science. Their anxiety has perhaps as much to do with the rapid changes in the nature of the

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organisation of science itself. The better management of science and scientists may help to relieve this anxiety.

We have made a study of the funding of the Science Base over the last ten years or so, especially in relation to the number of scientists and technologists involved. The popular view of a declining budget is not borne out by the facts. Whilst it is not easy to decide on the most appropriate index of inflation for the costs of research and development, it is broadly true that the level of science funding in universities and related research establishments has at least been maintained.

If we include the substantial increases in funding from non-governmental sources, then the total science budget can be seen to have increased markedly. Even so, within the science sector of higher education, the restructuring of, e.g. university funding procedures has almost certainly distorted and weakened the research support base.

The need to maintain better levels of equipment and of laboratory support has been lost sight of. To achieve this will require better management of priorities in higher education and that initiative should come from the academic scientific community itself.

The relationships between the scientific community and the Research Councils is a vital one. Research Council funding must remain the principal basis of funding scientific research in this country and the Councils carry the great responsibility of ensuring that the funding is properly distributed amongst groups and individuals on the basis of excellence, invention and promise.

The scientific community and the country as a whole has to understand better the nature of the demands made by rapid

organisational change. The dynamic steady-state and its need for a greater pace of investment and disinvestment imposes considerable strains and greater costs on any organisation. This is particularly so on research groups at the leading edge of technology. This need can be met more easily by larger research groupings and this need not be at the expense of the individual researcher.

These assertions aside, the findings of our survey are that over the last ten years the total funding of the science base has increased steadily and that the salaries of those involved has at least been maintained in real terms. The number of scientists has also increased markedly, much of this increase being at the junior postdoctoral level. Beneath these monotonic changes lie marked variations in subject content, the rise of molecular biology being the most prominent. There is also clear evidence of the intentions of the young graduate to look ever more widely across the range of career prospects. The loss to the science base is undoubtedly a gain for the other sectors.

But salaries elsewhere in economy have risen in real terms.

Given, then, these reassuring factual findings, it remains to enquire why the staff of the Science Base, namely academic scientific community, sees itself in such a bad light. One cause of its low morale is the persistent campaign to talk itself down by mistakenly believing that Britain can be best at everything. Another cause is the uncertainty attaching to university funding itself. The level of morale needs to be improved for the sake, as much as anything, of persuading more of the young to see science as the career for them.

The solution is better management and a better understanding of that management. The voice of that management has to be that of the University Funding Council and the Research Councils. Good relations between these bodies and the University Community are essential if research is to be

encouraged and the country to be reassured that research and science and technology remains one of its most important and rewarding pursuits.

RECOMMENDATIONS

1. The critical importance of scientific knowledge and of the capability derived from scientific and technological skills, needs to be reiterated and seen to be one of the essential bases of a thriving economy.

2. Government spending on the science base should therefore be maintained and not allowed to decline, for example, as a percentage of the nation's wealth expressed as GNP.

3. The funding of research should be distributed largely on the basis of peer judgement and, therefore, largely in the hands of the research councils. They will have particular regard for the initial funding of young and newly appointed staff.

will they?

4. They (the research councils) will also have regard for the capacity of individual universities to deliver the well-found laboratory on which significant and continuing research groups will depend.

SCIENCE BASE STUDY GROUP

INTERIM REPORT

INTRODUCTION

1. The term 'Science Base' has many definitions. The definition adopted here was the envelope of resources spent by Research Councils plus those spent in HEIs on research from all sources: UFC, PCFC, Government Departments, other public sector organisations, private organisations (including industry) and overseas organisations.

2. We believe that the United Kingdom needs a strong and healthy science base. The knowledge and capabilities deriving from the science (and technology) base are key factors in determing the productivity and effectiveness of our economy and public services, our health and our ability to understand and adapt to environmental and social change.

3. The health of the Science Base has become a matter of considerable debate. There is an articulate lobby which argues that science in the UK has become increasingly underfunded in comparison with that in other countries. Dissatisfaction with the level of science funding is linked to a more general complaint about the funding of higher education, especially of universities. The spectre of a 'brain drain' of outstanding research scientists is frequently raised, as is the assertion that without increased support of the Science Base Britain's economic prospects will be impaired.

4. Another, less vocal lobby argues that at least some of the dissatisfaction is the result of rapid changes in the nature and organisation of science itself. The exponential nature of the unfettered expansion of scientific knowledge is bound to collide

with the finite nature of resources. Expectations in many areas of human activity will therefore be increasingly disappointed until the implications of the dynamic steady state are understood. In the public debate there is also an anti-pure science lobby which argues that Britain has failed to achieve the best balance between pure science and exploitable science. The assertion is made that the intellectual force of pure science has undermined the respect, especially in the young, for the applied sciences and technology.

5. Somewhere between these extreme views there lies a balanced view of what Britain should be investing in the various areas of scientific activity, including its exploitation. This study has attempted to answer the question 'Have we got that balance right?' It has done so by defining the parameters of the enquiry, by examining the relevant data of the last ten years, and by drawing attention to some studies of the principles involved.

6. Two structural factors dominate the Science Base. Firstly, funding has come mainly from Government. Recently, spending restraints have been imposed as part of a wider policy of containing public expenditure in real terms. Secondly, science is essentially international, because the world effort is, and has been, continuing to increase. The UK has, therefore, a diminishing fraction of world science. At the same time competition is strong and intensifying.

7. Over the last ten years the responses required from the Science Base were recognised to include:-

a. concentration on those areas of science where the UK could make the best contributions and use resources most effectively; and

b. better organisation of the efforts in these areas to, at least, keep up with international competition.

8. Thus, processes of radical adaptation and change have been needed at a time when growth in resources was limited. It was also a period when opportunities and fields of interest have multiplied enormously, especially in the field of the life sciences, but also in other areas such as materials and in advanced computer science.

9. Additionally, laboratory facilities for the pursuit of science in fundamental particle physics and astronomy have required greatly increased allocations for more and larger experimental facilities. These factors have put increasing strains on the management of the Science Base and of the personnel employed therein. There is a widely held feeling that the dual support system by which the Research Councils and the UGC provided funding for the Science Base has faltered in recent years, primarily because the proportion of university income coming from the UGC has fallen.

10. The Study Group took as a starting point a review of the changes in funding and manpower of the Science Base over the last ten years. It commissioned a report from SEPSU to collect together information for the decade 1977-78 to 1987-88 and include later data where available.

11. The SEPSU report (Annexed) on which this commentary is based shows that the income of the Science Base from all sources increased by 30% in real terms in the decade 1977/78 to 1987/88. DES funding of the Science Base has increased in real terms over the same period by some 17%. This is shown in Table 2.2 where the GDP deflator is used to remove the average effects of inflation and the data are presented as a comparison in terms of 1987 values. Government funding has however declined as a percentage of GDP and is expected to decline further (page 4),

although income from all sources has approximately kept in step with GDP. The proportion of non-DES funding of the Science Base has increased from 19.7% in 1977/78 to 27.3% in 1987/88.

12. The part of the Government grant to the UGC which goes to support the Science Base (in this case the universities) is estimated to have increased by 16% in real terms (GDP deflator) between 1977/78 and 1987/88, though nearly all that increase will be lost by 1990/91; but the figures should be taken with considerable caution in view of the uncertainties in the estimating process (Table 2.2). The Science Budget (essentially through the Research Councils) increased by around 19% in real terms between 1977/78 and 1987/88 (table 2.2) and will increase by a further 15% by 1990/91. Also the expenditure per head of all university staff involved in S & T research has increased in real terms since 1981/82 (table 5.2) by 17%.

13. The research income of the universities, excluding UGC contributions but including contributions from the Science Budget and other sources, has increased by 78% in real terms from 1980/81 (table 2.4). This is due to the increased contributions from the Research Councils and to a steep increase in funds from industry, charities and other Government Departments over the past decade. Some of the latter sources of funds have brought with them additional constraints for the universities. Because of the dual support system Research Councils and charities were not expected to meet the full cost of the research they support; and industry and other government Departments also very often did not do so. The shortfall had to be met from the UGC grant, and there were increasing strains because the shortfall has presumably increased by roughly the 78% quoted above. In addition, industrial funding may imply more dirigiste research programmes and support from OGDs may also require research to be within the objectives of the customer Department.

GDP and UPPI Deflators

14. The GDP deflator, used in arriving at real price trends in the tables, is designed for the national economy as a whole. In the case of specialised activities such as research in universities it may not be the most appropriate factor to use. An alternative is the Universities Pay and Prices Indicator (UPPI) which although covering other activities than research is based on actual expenditure. Both deflators are used in tables 2.1 and 2.2 to show the critical effect they have on the time trends. The comparison with GDP can be defended on the grounds that universities should share national income on the same basis as other sectors of the economy. However, note should be taken that this does not reflect the changes in actual costs incurred in research. In general this paper will use figures normalised by reference to GDP deflator, since this is general Government practice.

The 30% increase referred to in para 10 is 10% using the specific deflator.

International Comparison

15. The ABRC has conducted a survey of funding for the Science Base in a number of competitor countries, particularly US, Japan and the EC. The conclusion from these studies is that although there has been substantially increased funding in the UK the increase is less than that provided by some foreign Governments for their Science Bases. There are many possible explanations and comparisons of statistics. Even the use of OECD purchasing power parity comparisons presents difficulties. However, there is little doubt that these other countries have markedly expanded their basic science effort in the last decade. The result of this has been an increasing competition between countries and, inevitably, a relative decline in the UK's share of world science; whether judged by Nobel prizes, patents, citation indices or output of peer reviewed scientific papers. The pressure on UK university researchers to compete has produced an atmosphere in the universities which accentuates

pressures on funding, salaries, and competition for talent. This is in spite of a fair amount of evidence that in some aspects conditions have improved, for example the increase in the Science Budget of 15% in real terms between 1987/88 and 1990/91.

16. The basic problems as seen by researchers appear from both quantitative and qualitative evidence to be as follows:

a. lack of proper funding for well-found laboratories, including technical support;

b. more dirigiste research funding from the Research Councils as they try to be selective, for example towards trends in engineering and science;

c. relative decline in the funding for core sciences;

d. decline in salaries for academics relative to other employers leading to difficulties in recruiting and holding good permanent staff;

e. the rapid increase of research assistants and post-doctoral staff with temporary positions;

f. lack of money for equipment and

g. the lack of funds for small scale grants and for seed-corn research.

It is instructive to look at each of these in turn.

UGC Funding of research

17. Over the period in question the UGC funding of universities was in the form of a block grant which each university could spend as it chose. The figures of table 2.2 are derived by assuming that some 38% of resources (ie block grant plus home student fees) was for research, although it is recognised that there are large variations between subjects, and in the disbursement arrangements within different universities. Various surveys suggest that the ratio of expenditure from resources on teaching to that on research is about 63:37, and that this has not varied substantially during the last twenty years. UGC estimates for individual subjects, based on peer judgement, range from 50:50 in physics to 80:20 in dentistry.

18. The purpose of the dual-funding system is to ensure that the UGC block grant funds the 'well-found' laboratories. More specifically this includes the following contributions -

a. the salaries of the academic staff who direct and lead the research,

b. the buildings in which the research is done, including their services and maintenance,

c. the library facilities,

d. about half the technicians,

e. consumables, and much of the apparatus to be looked for in a well-found laboratory,

f. the central administration,

g. much of the costs, other than maintenance, of research students and

i. all the research which fails to attract outside grants.

The proposed transfer in 1991 of £70m from UFC to the Research Councils to fund all of these elements in connection with research council grant work changes the boundaries. It concentrates this element directly to researchers supported by these grants. This obviates the risk of dilution of these funds by diversion elsewhere by the distribution processes of individual institutions.

19. The budget pressure on universities has meant that savings have had to be sought in all areas. As it is usually easier to reduce spending on things rather than on people, the 'things' in the list: ie building services, maintenance, consumables and apparatus have experienced the most severe pressure.

Directed and Responsive Mode Research Council Funding

20. There has been an increasing trend in the Research Councils towards funding proposals in directed programmes. The concern of many researchers is that this may favour proposals which may not be as good value as those from the responsive mode. The figures for the SERC show that over the last few years the proportion of grant funding between responsive mode and directed programmes has been set at around a ratio of 1:1 for the Science Board and 3:7 for the Engineering Board, respectively. Another issue particularly concerning the SERC is the trend away from nuclear physics and astronomy towards engineering research. In 1977/78 expenditure by the Engineering Board of SERC was 15.7% of the total. By 1987/88 this has increased to 27.7%.

A good thing? or a bad thing?

21. A particular concern is the proportion of Research Council expenditure which is spent in the Councils' own

establishments. This mainly concerns AFRC and NERC where the situation is complicated. The figures on page 9 for SERC show that universities use a very high proportion of the facilities available in institutes (between 67% and 94% depending on which facility). Also for the SERC in 1977/78 the ratio of expenditure in own establishments to those in universities/other HEIs was 0.9 to 1 in 1977/78. In 1987/88 the ratio had fallen to 0.5 to 1 (Table 3.3). This reflects, in parts, the increases in the Engineering Board's grants (Table 3.4).

Core Science Funding

22. Although the question of the structural changes in research in HEIs is discussed later it is useful at this point to examine whether the core sciences have lost out over the decade. As far as the Science Budget funding for core sciences is concerned there is some evidence of a relative decline in recent years. The proportion of SERC funds that went to its Science Board rose from 23.2% in 1977/78 to 32.0% in 1980/81 before declining again to 25.5% in 1987/88. There seems little evidence that any substantial part of core science funding intended for spending at universities has gone to research institutes. SERC say that if the facilities are to be used as part of a grant they allocate a given number of days and add this to the grant. The costing of the research institutes in the SERC is done under a separate heading (page 9 and table 3.3). The feeling of a decline in support for core sciences probably arises from the deterioration noted above in the well-found laboratory and support for seed corn science from the UGC grant. It also may reflect a concern that more of the SERC's funding is regarded as dirigiste and in favour of large groups and hence large grants.

Unfunded Alpha Project Proposals

23. Tables 5.3 show that the Research Councils are unable

to fund all the alpha quality research proposals which are made to them. For all Research Councils in 1980/81, 86% by value of alpha rated research grants were funded. By 1987/88 this had fallen to 62%. These data is a clear indication of the vigour of the Science Base in reacting to the expanding opportunities in research, and to international competition. As noted earlier the Science Budget has been growing strongly in the last few years and to a fair extent this has meant more money available for grants, but clearly not enough to cover all opportunities. In some instances projects are probably re-submitted and some may go ahead in any case with funding from university departments and from external sources, although the former are being squeezed as already indicated. It is therefore difficult to generalise, but the number of unfunded alpha projects can be a healthy sign and means that those projects which are selected are very good. In a recent Parliamentary Answer (22 January 1990, Cols 495-6) the total value of the alpha-rated research grants funded for all 5 Research Councils was given as £185.5m. A further £87.5m would have been required to fund all alpha-rated applications in 1988-89. Some further allocation to research grants may be warranted, but a policy of selectivity will mean that some alpha-rated applications will not be funded.

Salaries

24. A major element of pressure on budgets has been salaries. As 1978-79 was a period of high inflation, comparisons over the decade depend crucially on the month in which the comparison is started. Over the decade the index of non-manual earnings increased by 35% (DEmp figures); scientists, engineers, university staff and teachers were among those professional groups which were left behind. For example, the stipend of the typical university lecturer, taken as 39 years old, has increased by about 10% in real terms (page 3).

25. Most individual academics have done better than this because of scale increments and promotions; but the same could be said in any profession. Since the average age of academics has increased substantially over the decade, the average cost of an academic to his employer (the university) has increased much more than 10% in real terms. Despite a 7% decline in the number of academic staff funded from block grant since 1977/78, an increasing proportion is spent on academic salaries and this trend seems likely to continue. Table 3.7 shows that expenditure on permanent academic staff salaries increased by 5.9% in real terms between 1980/81 and 1987/88. Over the same period, expenditure on technical staff decreased by 11%. Total UGC funded pay expenditure has remained at around 67% of total recurrent expenditure.

Ageing of university staff

especially drop in under 40s.

26. The skewed age profile of permanent university staff [Figure 4.4(iii)] is, in all subjects, a matter for serious concern, despite the alleviation produced by the New Blood Scheme and the New Academic Appointments Scheme. The increase in average age is most pronounced in scientific faculties [figure 4.4(ii)]. This could have been expected to have an adverse effect on the quality of scientific research but it seems not yet to have had any dramatic effect, perhaps because of the increasing number of young staff funded from non-UFC sources (figure 4.4(v)). Most of these staff go from one short-term contract to another, and there is increasing concern over the lack of credible career patterns for them. The same lack appears to be increasingly to be discouraging able undergraduates from going on to research.

Migration

27. Data on migration to and from overseas of academic staff in the UK show that in every year since 1983/84 there has been a

net inflow into the UK. By grade, however, there are marked differences and there is a consistent outflow of staff in the reader/senior lecturer grades. There is no evidence of a net loss of professorial staff. In 1986 there was in fact a net increase into the UK of such people, according to the latest USR figures.

Short-term Research Assistants

28. The total number of full time academic staff in the science base in 1988/89 is 18.5% higher than in 1977/78 (table 4.2). The expansion has been 36% for biology, 34% for mathematics and computer science and 29% for engineering and technology but less than 5% in physical science and agriculture. However, the number of full time staff funded from general university funds (UGC - ie essentially long term staff) fell by 7% between 1977/78 and 1988/89. The actual loss since 1980/81 is around 3600 posts.

29. There has been a very substantial increase in short term appointments funded by other sources such as Research Councils, Charities and industry. These have increased by nearly 100%. In science short term posts have increased from 22 to 40% of all science staff. For engineering the figures are similar. Short-term staff are young and 86% of them are doing full time research. There has been an increasing tendency for PhD students to take salaried research assistant posts in preference to less remunerative studentships. This trend, coupled with the increase in external funding of academic research, is an important factor in the growth of academic staff on short-term appointments.

Equipment costs

30. The Advisory Board for the Research Councils has reviewed the current state of equipment in HEIs (all universities and a sample number of polytechnics). The review,

which was conducted by PREST using a questionnaire technique, has shown that 86% of equipment is adequate or better. This equipment was mainly supplied by funds from the UGC (46%) and SERC (29%), other Research Councils and industry. The value of equipment was estimated on a replacement basis as £624m. 41% of it is less than 5 years old and 37% is over 10 years old.

31. The general conclusion from the survey was that at least £260m extra spend was required for current research and a further £200m for future plans. This has to be seen in the context of the survey returns reflecting optimum needs; and therefore perhaps going beyond the truly necessary. The main concern of researchers in the Science Base is that the cost of renewal plus necessary enhancement has increased much faster than either the retail price index or the index of deflation used by the Government. A very rough analysis from the PREST Report based on age, replacement cost with equivalent and population indicates that costs have risen at about the same rate as the RPI. If the calculation is made for enhanced capability replacement, there is probably an increase of between 5 and 10% pa above inflation. The respondents to the PREST survey indicated that they have a higher priority for new staff than for new equipment. In some cases it was not equipment in the range £10,000 to £1m which was required but more to be spent on small scale items and consumables. It should be noted that the development of new techniques using sophisticated equipment has proceeded most rapidly in the biological areas and funding for equipment has caused particular problems there.

Size of Research Grants

32. There is concern that there is less available support now compared with ten years ago for small grants and for young scientists who have not made their mark sufficiently to get a research council grant. To some extent the gap is filled by the Royal Society research grants scheme (table 3.1) and grants from

charities and similar organisations. However, the proportion of SERC grants of less than £10,000 were 13% by number in 1988/89. The number between £10,000 and £20,000 was only 3% of the total in number and 1% in value. There are no figures to show that this situation has changed over the ten year period, but it remains a concern to some and will need special attention.

33. A possible solution to the lack of seed-corn research funding is to consider an earmarked amount as part of the UFC grant to universities. The advantage would be that it would be up to their departments to see how it is spent with perhaps a 3 or 5 year review. The main argument against is that it increases the amount of earmarked money and hence reduces the flexibility of the universities.

Other budget pressures

34. Besides pay and pay-related employment costs there have been other increasing pressures on budgets. For all Research Councils, superannuation costs have risen noticeably over the ten year period (table 5.1). Both they and universities have had to meet increased costs from restructuring and upgrading buildings to meet new fire, health and safety requirements. These demands have increased disproportionally, meaning less money spent at the bench - hence the squeeze. This is shown in table 2.2 by increasing the values to 1987 pounds using the UPPI index which is based on what universities actually spent. Over the twelve years up to 1989 the 14% real increase in GDP deflator terms of the DES spend is factored down to a 2% decrease in UPPI terms.

STRUCTURE OF RESEARCH

35. The organisation of science in the universities has changed considerably over the last 40 years and particularly over the last ten years. An increasing amount of research is now

conducted in groups, rather than by individuals, and the size of these groups is increasing. The reasons for this are many but two are important. Over the last ten years there has been an increasing trend in the universities towards more efficiency and better management, in order to optimise resources and to make the best cases in grant applications. It is received wisdom that increasing size can help to increase efficiency. The operation of IRCs may confirm this. Closer management does not always mean an hierarchical structure. There is qualitative evidence that federal structures have evolved as well but all with the aims of improving management efficiency.

36. The other driving force is the evolution of research equipment. As this becomes larger and more expensive it tends to draw to it larger and larger groups of scientists. Also these scientists will be working full-time to optimise the use of expensive installations. The driving force is competitiveness. The downside of this group working is the reduction of research carried out by individuals with new ideas. The overall feeling is that working in groups has been brought about for mutual assistance. It may be the required solution in the face of international competition but the number of small groups is likely to decline.

SUMMARY

37. In a period in which Government policy has been designed to contain public expenditure the resources available to the Science Base have held up reasonably well. It has developed alternative sources of income, and has undergone substantial changes of character and organisation to adapt to changing circumstances. These changes have however left a legacy of financial burden that reduces the room for manoeuvre with available resources. There is also a legacy of expectations and perceptions dating from earlier periods that similarly cannot be met.

Lord FLOWERS

21/3

FILE KK

C/Economic/Flowers

Ack

10 DOWNING STREET

LONDON SW1A 2AA

From the Private Secretary

CF
You may like to take this on now. Reply due in today. 21/3

SIR JOHN FAIRCLOUGH
CABINET OFFICE

I enclose a letter to the Prime Minister from Lord Flowers, dated 6 March, following up her reply last November to the report of the House of Commons Select Committee on Science and Technology. I should be grateful if you could arrange for a draft reply for the Prime Minister's signature to be prepared.

BF 11

I am copying this minute to the Private Secretaries to Members of E(ST) and to Sonia Phippard (Cabinet Office).

PAUL GRAY

7 March 1990

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MJ 1

ecdes

c: MRC

10 DOWNING STREET

LONDON SW1A 2AA

From the Private Secretary

28 February 1990

THE MRC's CLINICAL RESEARCH INITIATIVE

The Prime Minister has seen your Secretary of State's minute of 27 February and is content for the proposed terms of reference for the steering group to be announced.

A copy of this letter goes to Stephen Crowne at the Department of Education and Science.

Dominic Morris

Andy McKeon Esq
Department of Health

CONFIDENTIAL

ea

CABINET OFFICE

70 Whitehall London SW1A 2AS Telephone 01-270

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Our ref: Qe 0107

File ref: ST 140/1

12 February 1990

Mr S Webb
PS/SoS
Ministry of Defence

Dear Mr Webb,

ACOST REPORT: DEVELOPMENTS IN BIOTECHNOLOGY

Paul Gray's letter of 6 February noted that the Cabinet Office would be forwarding copies of the ACOST report on Developments in Biotechnology. Your Department's copy is attached.

The Prime Minister has given ACOST permission to publish the report subject to any factual corrections which the Government advises are necessary. Please let me have these (or a nil return) by Wednesday 28 February.

The Government response to the report will be published separately. Please let me have your Department's contribution to this by Friday 23 March. The collated response will be cleared by officials, then by E(ST) Ministers, before the Prime Minister sends it to Sir Francis Tombs.

I am copying this letter to PS/E(ST) Ministers (for factual corrections and for contributions) and to Sir Robin Butler (for information).

Yours sincerely

Ian Dixon

Ian Dixon
S&T Secretariat
Cabinet Office

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ADVISORY COUNCIL ON SCIENCE AND TECHNOLOGY

REPORT

on

DEVELOPMENTS IN BIOTECHNOLOGY

January 1990

ACOST SECRETARIAT
Cabinet Office
70 Whitehall
LONDON SW1A 2AS *Tel: 01 270 0105*

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Report of the ACOST Emerging Technologies Committee

DEVELOPMENTS IN BIOTECHNOLOGY

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BIOTECHNOLOGY REPORT

SUMMARY

i. This study has been carried out by the Emerging Technologies Committee of ACOST in order to review progress in biotechnology since the Spinks Report was published in 1980. The Spinks Working Party forecast the increasing importance for biotechnology, and its development into a key technology for the world economy during the next century. Areas of priority were identified and recommendations were made to improve the coordination of the UK Government's funding in biotechnology to assist the future commercialisation of scientific developments. This ACOST report does not address all the issues considered by Spinks.

ii. Biotechnology is a collective term for a wide range of scientific and industrial disciplines. The potential benefits to society are considerable. These include: the provision of better methods of health care offered by new vaccines, drugs and diagnostic reagents; environmental improvements from the reduced use of fertilizers, pesticides or other chemicals and from the development of environmentally safer chemicals; increased food production; and improved food quality and consumer choice.

iii. Biotechnologically-derived pharmaceuticals and diagnostics are beginning to arrive on the market. Our assessment convinces us that biotechnology remains a topic of immense potential, requiring continued long term investment in the science base.

iv. Although our industry is beginning to recognise the scale of opportunities presented by biotechnology we are concerned that the UK is failing to exploit fully its strengths in the biosciences. Our potential for leadership in many areas is being eroded as leading US and Japanese companies invest heavily worldwide. Major UK developments, for example in the plant sciences, are

increasingly being exploited by competitor multinational companies, aided by the recruitment of UK skilled personnel.

v. Since multinational companies are free to develop their R&D wherever they find strong and appropriate science a strong UK science base will help to maintain and generate manufacturing activity by national and international companies in this country.

vi. To succeed in this rapidly developing discipline UK industry faces the challenge not only to evolve the scientific and technological abilities but also to respond quickly to scientific advances and the new commercial opportunities.

vii. We note the initiatives that have been taken in response to the Spinks Report which have been helpful in maintaining the UK's position in an increasingly competitive international field. The Research Councils have continued to support much of the fundamental biological science upon which commercial prospects depend. The DTI has helped to coordinate Government Departmental policy in biotechnology through the Interdepartmental Committee on Biotechnology (ICBT). However better coordination between the Research Councils is required, as the Morris report to the ABRC has highlighted. The DTI and SERC have been instrumental in establishing 'club' activities and several LINK programmes have been approved recently to further encourage collaborative research and technology transfer in biotechnology.

viii. Technology transfer is proving successful in certain areas. Examples include: the transfer of the MRC developments in recombinant DNA and hybridoma technologies to Celltech and the establishment of the MRC collaborative centre at Mill Hill; the transfer of AFRC research in plant biotechnology to the Agricultural Genetics Company and research in animal biotechnology to the new company Animal Biotechnology Cambridge; and the collaboration between Leicester University and ICI in genetic

fingerprinting. However, the commercial benefits to accrue from biotechnology have not been as rapid as the Spinks Working Party envisaged with few companies presently making a profit from these new developments.

ix. The next phase of development in biotechnology is likely to lead to the engineering of higher levels of biological organization; the engineering of pathways and cells. The future production of cells with particular desirable characteristics, 'designer cells', could lead to novel treatments for diverse diseases.

x. Advances in molecular biology now create the prospect that serious genetic defects, responsible for the substantial burden of ill health brought about by inherited diseases, will be corrected by gene therapy. Advances in embryonal stem cell research and the experimental investigation of transgenic animals will bring nearer the possibility of restoring normal function to diseased tissue. The UK has strengths in these areas and is well placed to take a leading position.

xi. Future success in biotechnology will depend on strengths in many supporting scientific areas; there is some danger that concentration on newer molecular genetics has not been balanced by support of the appropriate related scientific areas. For example, the initiatives to set up an IRC and a LINK programme in protein engineering are considered adequate to maintain the UK's scientific pre-eminence in that topic but the ability to gain commercially will also depend on the supporting skills such as crystallography, 2 dimensional NMR and molecular modelling. It is important to ensure that these areas are strongly supported. There is also a need for well trained clinical research workers with knowledge of biotechnology and molecular biology. Exploitation of plant biotechnology will require more research into plant biochemistry and plant physiology. Further research in microbial ecology is

required for full understanding of the consequences of releasing genetically modified organisms into the environment.

xii. Biotechnology is affected by skill shortages exacerbated by its multidisciplinarity and pervasiveness, its recent and rapid commercialisation and the high level of skills required by the industry. Selective skill shortages have existed for some time in areas such as plant molecular biology, biochemical engineering and downstream processing, cell biology, enzyme technology and microbial physiology.

xiii. Other barriers to effective exploitation arise from uncertainties about patenting. The level of commercial success, and hence the rate of investment and development, will be critically dependent on good patents which are upheld in court. The status of European patenting is complicated at the present time but a draft Community Directive to clarify the position is presently being considered.

xiv. Questions on safety, ethics, the environment and welfare and public perception will influence the direction and rate of progress. The Health and Safety Executive's Advisory Committee on Genetic Manipulation (ACGM) have established a good model for ensuring public safety without undue hindrance to scientific research and industrial development by having a wide representation of views and keeping the public informed. This approach has served to prevent much of the severe adverse public reactions which have accompanied certain developments in the US and parts of the EC. However, some Government Departments are, at present, seen to be taking a cautious role in respect of public consultation. This could lead to problems which will restrict the introduction of many potentially beneficial developments. Government Departments should be sufficiently alert to the ethical issues that are likely to cause future concern.

xv. Wider public debate is required but in order to prevent adverse public perception affecting unrelated areas it is essential to convey to the public that the discussion of possible risks and the potential benefits should not be global but be on a case-by-case basis. Thus, debate on a topic which has profound ethical issues associated with it could be continued and new knowledge could be assimilated without holding up developments in commercialising distinct entities.

RECOMMENDATIONS

We recommend that:-

a. Government Departments should take a more proactive role in biotechnology (appendix A).

b. A programme of balanced information should be provided to the public on major aspects of biotechnology, such as genetic engineering (appendix A, p.15). This would be of interest to both the scientific and medical community and to industry where the lack of such a programme contributes to a major market imperfection. The Interdepartmental Committee on Biotechnology (ICBT) should coordinate the interests of other Government Departments in this area. Elements of such a programme should include:

- The commissioning by Government of an independent body such as The Royal Society or a charity (eg. The Leverhulme Trust or The Nuffield Foundation) to prepare a booklet providing reliable information and analysis for the public (appendix A, p.16).

- In the longer term, increasing the general level of understanding of such matters through education in schools. The DES should consider how to achieve this.

- Consideration by the ICBT of how to disaggregate those areas and industrial developments which have few or no safety and/or ethical implications from those which have and to convey information on these divisions to the public.

c. Inter-research council coordination of biotechnology should be strengthened. For example, an opportunity exists for the AFRC and SERC to consider a coordinated programme of molecular, biochemical and physiological studies in the plant sciences (appendix B, p.13).

d. UK research institutions should explore ways of taking a more European perspective and should determine how they can gain greater added value for the UK from collaboration with European partners.

e. Increased industrial support for biotechnology in UK universities and research institutes is required in order to enhance the transfer of the considerable scientific expertise into commercial success (section 7.2.14).

f. As a matter of priority UK strengths in plant biotechnology should be reinforced (appendix B, p.12). Government, in conjunction with industry and the research community, should aim to provide guidance to those in universities and the research institutes on the balance between work of interest to industry and work to satisfy national requirements on environmental issues. Emphasis should be placed on stimulating research into isolating important genes and to learning how to manipulate them in plants of economic and scientific importance (appendix B, p.9). Further technical and economic assessment of the potential for producing chemicals from plants should be encouraged, for example antibodies (appendix B, p.13). The Priorities Board for Research and Development in Agriculture and Food might consider how to stimulate interaction between the agricultural and chemical industries (appendix B, p.13).

g. A strategic decision by Government and industry to support embryonal stem cell biology will consolidate our strengths and will complement the UK initiative in the research on the mapping of the human genome (appendix C, p.18). The MRC and the AFRC should consider how they might coordinate an initiative to provide increased support in this area of biological research, taking into account the strengths that exist in the Cancer Charity supported Institutes. They should also continue to give priority to work in genome mapping and automated sequencing techniques.

h. AFRC, MAFF and DTI should give consideration to the development of a programme in embryo multiplication in cattle (appendix C,p.8); to applying biotechnology to the production of higher quality and healthier products (appendix C, p.8); and to the funding of a programme to encourage the development of efficient methods for the construction of transgenic mice and other laboratory animals (appendix C, p.14).

i. Manpower shortages should be addressed. The DES, the Research Councils and DTI should consider how to establish a coordinated approach with industry for the future provision of manpower needs in the biotechnology related industries (paragraph 7.2.17).

j. Increased support is required for the related skills in chemistry which UK industry will require to take full advantage of the initiatives in protein engineering. It will be important to sustain the UK's strengths in crystallography and to enhance support for 2-D NMR and molecular modelling (appendix D, p.10). The Research Councils should consider this in conjunction with their funding of protein engineering. The DTI and SERC in their training role in for example the Teaching Company Scheme and the Integrated Graduate Development Scheme should also take action in this respect.

k. Consideration should be given to a detailed and systematic analysis of the ethical issues that surround certain aspects of genetic manipulation. This could possibly be by means of ad hoc Committees along the lines of the Warnock Committee (appendix A, p.13).

1. INTRODUCTION

1.1 Biotechnology is a broad term used to describe the production of innovative products, devices and organisms by exploitation of biological processes. Traditional biotechnology was based on enrichment and purification, modern biotechnology on the manipulation of genes and on the alterations of the genetic structure of cells. Much of its importance stems from recent advances in genetics and biochemistry and from the emergence of molecular biology.

1.2 Underpinning future progress in genetic manipulation will be advances in molecular genetics and the knowledge of genomes of organisms. Considerable national and international effort is being directed towards the mapping and sequencing of genomes. Whereas efforts have so far been concentrated on the generation of biologically important molecules the next phase is likely to lead to the engineering of higher levels of biological organization: the engineering of pathways and cells. The production of 'designer cells' is likely to be one of the major technological advances of the coming decades. The potential for health care is enormous, and the commercial opportunities will be considerable. These are scientific areas of great significance to the UK's future success in biotechnology and ones in which we are currently strong.

1.3 Biotechnology is an enabling technology : its power is based on its capacity to affect a wide variety of processes and organisms, and it is in turn driven by novel technologies. These are:

- Sequencing of genes and proteins

- Genetic engineering. The ability to cut and splice DNA, to move genes from one organism to another and to get them to work there.

- Fused cell techniques. The ability to fuse two cells, from organisms that will not cross sexually, to yield a novel cell, containing the whole or parts of the genomes of both parents. This is the basis of monoclonal antibody production, and of the production of novel plant hybrids.

- Protein engineering. The ability to alter the structure, and hence the properties, of proteins by manipulation at the DNA level (for more details see appendix D).

- Fermentation and cell culture techniques. The ability to grow large amounts of microbial, plant or animal cells.

1.4 These technologies have been used to bring about advances in several major areas of application including:

- Production of high value chemicals, mainly pharmaceuticals, including recombinant proteins in large amounts for medical use

- Production of intermediate value chemicals or of enzymes or organisms for their production

- Production of monoclonal antibodies for development of novel diagnostic techniques

- Production of novel plant species or higher plant yields (plant biotechnology, appendix B)

- Modification of animals (animal biotechnology and transgenics, appendix C) and

- Detection of genetic variation in humans (and the possibility of gene therapy).

1.5 This report by the Emerging Technologies Committee of ACOST (see appendix E for the membership) assesses the recent progress in biotechnology in the UK since the Spinks Report was published in 1980. The present opportunities and the potential for the future are considered and we appraise the present UK position relative to our major competitors. We identify scientific areas of strength and weakness in the UK, highlighting the possible impediments to successful exploitation and make a number of recommendations accordingly. More detailed examinations of plant biotechnology, animal biotechnology, protein engineering and a number of non-technical factors which will influence the way in which the technology develops, are presented as separate appendices.

1.6 Views have been sought from a number of experts in the field during the course of this investigation, appendix F.

2. THE SPINKS REPORT

2.1 The present UK Government R&D funding policy in biotechnology is largely based on recommendations of a Joint Working Party on Biotechnology of ACARD, ABRC and the Royal Society, which reported in 1980 (the 'Spinks Report').

2.2 The Spinks Working Party concluded that biotechnology would have an increasing influence on diverse activities such as food and animal feed production, provision of chemical feedstocks, waste recycling, pollution control, medical and veterinary care and that it would be of key importance to the world economy in the next century. The Working Party highlighted the opportunities for the renewal of various existing industries in the UK, and the creation

of new ones, and made a number of recommendations for the UK to benefit. Increased support for biotechnology was called for and a number of areas were identified as showing particular potential, with a recommendation for priority attention. These were:

- genetic manipulation
- enzymes plus enzyme systems
- monoclonal antibodies and immunoglobulins
- waste treatment
- plant cell culture and single cell protein and
- production of fuels.

2.3 The Spinks Working Party also recognised the difficulties in managing research in this multidisciplinary subject. The report recommended 'a joint committee for Biotechnology with the support of a Director/Coordinator, to stimulate new projects in the Universities'. Increased communication between academic scientists and industry was also recommended.

2.4 Concern was expressed in the report that, in general, British industry seemed less able, less willing and less well informed of the need to take advantage of the potential of biotechnology. A policy of 'technology-push' progressively giving way to 'market-pull' was recommended to enable biotechnology to grow in a coherent fashion. The setting up of a new publicly funded biotechnology company was recommended.

3. PROGRESS SINCE THE SPINKS REPORT

3.1 In the years that have elapsed since the Spinks Report considerable technical and commercial progress has occurred. The predictions of the Working party for enzymes and enzyme systems were about right and advances in monoclonal antibodies and in genetic engineering have been rapid. Despite the strength of the

UK science base, it is disappointing that yeast genetic engineering, and that of other microorganisms relevant to the important UK sector of food and drink processing, have received little industrial support compared with the interest shown overseas. Developments in waste treatment and fuels have not lived up to the predictions of nine years ago because of unfavourable market assessments. Progress in plant cell culture has been hindered by the difficulty in obtaining sufficiently high product yield in culture.

3.2 Plant and animal biotechnology were given less prominence by the Spinks Working Group, but are now showing great potential. Detailed investigations of these two important areas are presented in appendices B and C of this report.

3.3 A new technology based on gene manipulation has evolved in the period since 1980. Throughout the 1960's and 1970's a considerable amount of research had been carried out on mutationally altered proteins. The direct manipulation of protein led to the semisynthesis of human insulin in 1979. However, the classical molecular genetic approach was slow and laborious and the direct chemical synthesis of proteins was only possible for small proteins. New techniques for site-directed mutagenesis led to the ability to alter the DNA sequence of a gene and to express the altered protein in living cells. Protein engineering has expanded rapidly since the first genetically engineered enzyme was published in 1982.

3.4 Protein engineering can, in principle, create an unlimited series of artificial proteins modified on the basis of rational predictions from knowledge of three-dimensional structures. The UK has led scientific developments in this new technology. As well as providing a powerful new research tool to evaluate the structural basis of the function of a protein, there is potential for commercial application by engineering proteins for industrial

enzymology and for use as new medicines (see appendix D).

3.5 Several major scientific discoveries and technical breakthroughs in molecular biology have occurred in the years since the Spinks Report. Two have been the subject of the latest Nobel prizes in Medicine and Physiology and in Chemistry. These are (i) the discovery that the genetic defects underlying cancers, the oncogenes, turn out frequently to subvert normal cell signalling and growth control processes and that oncogenes are mutated or otherwise malfunctioning normal gene coding for specific elements of cell regulation and (ii) the finding that RNA can have enzymic activity, previously thought to be an exclusive property of proteins. Each of these advances offers potential for application. Another development of major importance is gene amplification (PCR, polymerase chain reaction) that allows a specific gene to be copied a million times or more in a simple test-tube reaction; this is based on the ingenious use of DNA polymerase isolated from a thermophilic bacterium, and resistant to near boiling temperatures. PCR has major implications for all aspects of molecular biology including diagnostics, epidemiology and human genetics as well as being a major aid in basic research.

3.6 The Spinks report was, in general, too optimistic about the time scale for the transfer of the research into products; some diagnostics and therapeutic drugs have appeared but much of the potential is only now beginning to be realised.

3.7 Although the setting-up of a Joint Committee for Biotechnology, including all the Research Councils, was not achieved a number of initiatives resulted from the Spinks report. The Interdepartmental Committee on Biotechnology (ICBT) was established in 1982 under the chairmanship of the Government Chemist to 'provide a focus for biotechnology in Government and to stimulate its development'. The MRC, with National Enterprise Board involvement (now the British Technology Group, BTG) catalysed

the founding of Celltech in 1980. This company has developed into one of only two medium-sized UK biotechnology companies. The MRC have established a Collaborative Centre for Industry at Mill Hill. The SERC Biotechnology Directorate was set-up in 1982 as a strategic vehicle with a strong industrial influence. The SERC published a review of its activities in December 1988. The review panel concluded that the Directorate had made significant achievements in the support of biotechnology research. These included progress in scientific and engineering research, the fostering of links between the disciplines involved, the encouragement of industrial participation in collaborative pre-competitive research programmes, the transfer of results from basic research to industry and the provision of trained manpower. The panel recommended to the SERC that it continue to support biotechnology through a separate Biotechnology Directorate and that it should plan to expand its support for research and training in the subject.

3.8 Other recent initiatives in biotechnology include the setting-up of a joint SERC-DTI Joint Advisory Board on biotechnology, to which other Research Councils have been invited to be represented. This will cover the span of their respective interests in biotechnology. Several relevant IRCs have been established; in Molecular Science and Molecular Medicine, both at Oxford, Transgenic Animal Biology at Edinburgh, Protein Engineering at Cambridge and Cell Biology in London. SERC has funded two major biochemical engineering centres, similar to IRC's, at Birmingham and UCL. SERC has also operated a number of research clubs co-funded with industry such as those in Protein Engineering and Animal Cell biotechnology. DTI has funded similar clubs as well as awareness Clubs for industry such as BIOSEP (Downstream processes in biotechnology) and BIOTRANS (Biotransformations).

3.9 Another recent initiative is the establishment of collaborative LINK programmes between industry and academia in the

following areas; Biotransformations, Eukaryotic Genetic Engineering, Protein Engineering, Selective Drug Delivery and Targeting, the Control of Plant Metabolism, Biochemical Engineering and Molecular Sensors. The approved Government commitment for these programmes totals £24.7M, split between DTI(£13.45M; all programmes), SERC(£8.7M; all programmes), AFRC(£1.05M; Plant Metabolism, Protein Engineering and Molecular Sensors), MRC(£1.0M; Drug Delivery and Protein Engineering) and MoD(£0.5M; Protein Engineering). This will be matched by an equal amount from industry.

3.10 The SERC report of the 1988 Biotechnology Review Panel considered that more attention be given to collaboration between the Research Councils. They argued that the present fragmentation is to the detriment of biotechnology and to the efficient transfer of the basic discoveries to industry. To a large extent it was this problem in organisation of research in the biological sciences which led to the 'Morris Report', commissioned by the ABRC.

4. SUMMARY OF THE PRESENT DEVELOPMENTS IN BIOTECHNOLOGY AND POTENTIAL FOR THE FUTURE

4.1 Early expectations of wealth creation from biotechnology were slow to be realised and only lately have a significant number and volume of biotechnology-generated products reached the marketplace. These include human insulin, human growth hormone, alpha interferon, tissue plasminogen activator (tPA), interleukin-2 and certain animal and human vaccines. One of the benefits of genetic engineering was the speed with which it allowed novel growth factors for animal and human cells to be identified, characterised and produced in large amounts. Some of these have direct therapeutic use and a variety of growth factors (erythropoietin (EPO), which cures the anaemia of kidney failure, colony stimulating factors and epidermal growth factor) are already in

clinical use or are expected to reach the market soon. A number of hormones, lymphokines (which regulate immune responses), and therapeutic monoclonal antibodies are also expected on the market within the next few years.

4.2 Other growth factors allow differentiated cells to be grown in culture, often indefinitely, and will make cellular therapies more feasible. With the aid of this research genetic therapy of somatic cells is now feasible.

4.3 The implications of biotechnology for the agriculture and food industries are great with genetic engineering of crops, fertilisers, pesticides, veterinary drugs and vaccines, and genetic engineering of animals to produce, for example, leaner meat or to enhance milk production. Prevention and treatment of diseases of fish have promise for fish farming.

4.4 The genetic engineering of viruses and bacteria also offers varied opportunities. Research on Baculovirus insecticides is directed at obtaining environmentally acceptable alternatives to chemical insecticides. New engineered-types of safe, reversion-free virus vaccines, as well as vaccines with a broader protective power are the subject of present research activity. Engineered viruses, involving other viruses as delivery systems, could be used for wild-life vaccinations (eg. for rabies). Engineered rhizobium offers opportunities to improve crop yields in Nitrogen-poor soils. Eventually, the genetic-engineering of protozoa, nematodes, fungi and other unicellular organisms may provide further opportunities.

4.5 Waste treatment and fuel production may also present opportunities as economic and related factors change. It is likely that custom-engineered microbes will eventually be produced which are more efficient for particular waste management tasks and which have lower associated risks than their natural counterparts. Potential applications include: the decomposition of

polychlorinated biphenyls (PCB's), chemical wastes, nitrates, pesticides and other agricultural additives that accumulate in the environment after normal use; the breakdown of highly resistant toxic organic chemicals; the treatment of groundwater to remove dumped pollutants; and heavy metal recovery.

4.6 Microbial mining is an area of potential future exploitation. The possibility of releasing hydrogenous materials from fossil fuels, including oil-bearing strata, is of particular interest.

5. MARKETS

5.1 Present and Future size

5.1.1 Data on current sales or of future markets are hard to collate and predictions are uncertain. A report in the Economist, April 30 1988, estimated the size of the world biotechnology (new biotechnology) market to be $700M in 1987. Approximately $400M of this was for novel therapeutic drugs and about $300M was based on monoclonal antibody diagnostic kits such as AIDS tests. Although biotechnologically produced pharmaceuticals represent less than 1% of the present world-wide sales of the pharmaceutical industry (over $100 billion) a strong commercial future is expected. Celltech have predicted a compound growth rate of over 30% between 1988 and 1995, forecasting a market of $3.9 billion for biotechnologically derived pharmaceuticals in 1995.

5.1.2 Data quoted in the OECD report 'Economic and Wider Impacts of Biotechnology', 1989, and the United Nations report 'Transnational Corporations in Biotechnology', 1987, show an extreme range of forecasts for the world biotechnology market in the year 2000; varying from $9B to over $100B. These figures take account of the expected expansion in agricultural biotechnology, as well as other major market areas.

5.1.3 Early optimism resulted in considerable investment in biotechnology in the USA; a United Nations report on Transnational Corporations indicates that over $3B was invested in US biotechnology between 1974 and 1984. Investors have found they need to be more patient than originally expected, with few companies presently making profits. A report by Arthur Young entitled 'Biotech 89 : Commercialization' surveyed the 1037 US companies identified as having involvement in biotechnology in mid-1988. Only 26% of all respondents recorded profit and on aggregate the industry was losing money. Two thirds of diagnostic and therapeutic companies reported lower net income or greater losses on the previous year, suggesting decreased emphasis on the bottom line as companies continue to spend to achieve product development goals. However, a few early successes have helped to keep optimism high. On a year to year basis product sales were higher and assets rose by 32% for the survey population as a whole.

5.1.4 The wide variation in the prediction of the size of the market in the year 2000 reflects the difficulty in anticipating the scale of exploitation possible at this relatively early stage in the development of the new biotechnology. A number of additional factors will considerably influence future markets and must be taken into account alongside an assessment of the scientific opportunities. These include the regulations, nationally and internationally, for patents and a number of non-technical factors. In the following sections we summarise our assessment of the possible influences that these aspects may have on future developments.

5.2 Non-Technical Factors Influencing Future Developments

5.2.1 Public perception of biotechnology will have a major influence on the rate and direction of developments and there is

growing public concern about genetically modified products. Associated with genetic manipulation are diverse questions of safety, ethics and welfare. The Health and Safety Executive are responsible for an Advisory Committee on Genetic Manipulation which has considered all research requests relating to the potential release of genetically modified organisms. The Royal Commission on Environmental Pollution published in 1989 a major report considering the environmental implications of release of such organisms.

5.2.2 Present problems in Europe and the USA over bovine somatotropin (bST) highlight the difficulties that the industry could face. This genetically engineered hormone can give rise to increased milk production when injected into cows. Field tests have caused considerable controversy and increasingly there have been calls for a moratorium in Europe. An evaluation period, up to the end of 1990, has now been announced by the EC.

5.2.3 Debate on the safety, environmental, ethical and welfare questions raised by genetic manipulation will continue to be an important factor. We consider in more detail in appendix A how these aspects relate to our assessment of the development of biotechnology.

5.3 Patents

5.3.1 The level of commercial success in biotechnology, and hence the rate of investment and development, will be critically dependent on good patents which are upheld in court. Recent evidence from the US suggests that biotechnology patents are increasingly likely to be upheld by US courts.

5.3.2 The 1980 Chakrabarty decision of the US Supreme Court held that genetically engineered bacteria could be patented and the ruling continued that 'everything under the sun made by man' is

eligible for a patent. A US Supreme Court review of the Chakrabarty patent award highlighted for a public audience the fact that novel claims to the ownership of classes of living organisms were emerging and would continue to emerge from biotechnology.

5.3.3 The status of European patenting is complicated at the present time. The European Patent Convention (EPC), in force since 1977, states that patents cannot be granted on plant or animal varieties or essentially biological processes for the production of plants or animals; this provision does not apply to microbiological processes or the products thereof. In June 1989, the European Patent Office (EPO) examiners rejected an application for a patent on 'oncomice', transgenic mice which contain oncogenes, but the decision will no doubt be the subject of appeal. The American Patent Office had already issued a patent in 1988 to the Harvard Medical School inventors. Further complicating the situation are present interpretations on transgenic plants. While the EPC states that 'plant varieties' are not patentable, this does not necessarily mean that plant varieties are free of all patent rights and the European Patent Office have considered that where the invention is applicable to modifying plants of any kind whatsoever, the plants thus modified are of a higher classification than a 'plant variety' and have granted patents on plants.

5.3.4 A draft European Community Directive to clarify the position on biotechnology patents is presently being considered. This Directive, on the legal Protection of Biological Inventions, has the objective of providing a uniform regime of patent law in Europe that encourages biotechnology. It provides, for example, that there is no objection in principle to patenting living matter.

5.3.5 Concern has been expressed in the media about patenting of 'life forms'. However, a patent does not give its proprietor a right to make a product but a right to stop others from doing so. The right to make a product is given by the powers of regulatory

authorities.

5.3.6 Other important patent issues which require resolution include the question of the exhaustion of patent rights and the extent to which a patent on a novel DNA can be used to prevent that DNA being modified or linked to other DNA to circumvent the patent. It will be difficult to encourage innovation in transgenic animals unless some way can be found to prevent the progeny of the modified patented animals from being sold without consent of the proprietor of the patent.

5.3.7 As long as uncertainties remain, industrial investment in biotechnology in Europe will be constrained.

6. PRESENT OPPORTUNITIES

In the following sections we assess the present major opportunities for biotechnology, split into the areas of application mentioned in paragraph 1.4. Each has implications for the producers of appropriate equipment, offering substantial commercial opportunities. The UK has become weak as a supplier of key items of equipment needed for biotechnology and this is a particular aspect being addressed in the SERC/DTI Biochemical Engineering and Equipment LINK programme.

6.1 High Value Chemicals

6.1.1 The production of high value products, needed in relatively small amounts because of their high biological potency, was the first achievement of the new industry. Monoclonal antibody and recombinant DNA technologies have led to a number of medical applications of biotechnology and offer a wide range of opportunities for the future. While the former technology has had its greatest impact on diagnostics rather than therapeutics,

recombinant DNA has been used by the industry to produce some therapeutic agents such as human insulin, human growth hormone, erythropoietin, alpha interferon, tissue plasminogen activator (tPA) and interleukin-2 (IL-2). The risks of HIV and hepatitis stimulated efforts to produce recombinant plasma proteins of which a notable example is human factor VIII for treatment of haemophiliacs (now under trial).

6.1.2 These first generation biotechnology based drugs are natural proteins produced in large quantities by use of recombinant DNA techniques. Second and third generation drugs will be developed as a result of the interdisciplinary developments in pharmacology and biotechnology and opportunities include:-

- improved targeting of drugs, radioisotopes or toxins to tumours, blood clots or infections

- the stimulation or specific suppression of the immune system by synthetic antigens or biological immunomodulators

- improved DNA probe technology for viral diagnosis and for detection of genetic defects.

6.1.3 This will lead to improved diagnostics, vaccines and drugs. Among the medical benefits that are likely from these developments will be:

- improved treatment of cancer
- new approaches to the prevention and treatment of AIDS
- advances in cardiology, rheumatology and diseases of the central nervous system

6.1.4 Engineered proteins may be important antigens in eliciting protective immunity: this approach is central to strategies for

devising vaccines to the various important infectious diseases that afflict mankind. Short sequences that elicit antibody formation can be incorporated into another protein and presented, for example, as part of a polio virus to elicit antibodies against AIDS.

6.1.5 Biotechnology techniques are being utilised to study a range of systems associated with heart function and disease including cholesterol transport and biosynthesis, LDL-cholesterol receptors and factors involved in blood pressure regulation, leading to more effective therapies for cardiovascular disease. Major developments in cardiovascular drugs are occurring in two areas; in hypolipidaemics which reduce serum cholesterol and in fibrinolytics which dissolve blood clots. Tissue Plasminogen Activator (tPA) is the first major genetically engineered fibrinolytic drug, developed by Genentech, and a large market has been predicted for it. However, there is uncertainty over the patent and the wide ranging patent by Genentech has been successfully challenged in a British court. It is also uncertain how tPA will compare in practice with existing cheaper drugs or with potential competitors like Eminase (Beechams).

6.1.6 The development of engineering of higher levels of biological organization is imminent and can be expected to have substantial benefit. Cell receptors - structures on cell surfaces that react specifically with effector molecules that trigger, for example, cell growth - have been isolated and studied by molecular biological cloning techniques. The resultant improved understanding of receptors as well as other proteins which are involved in cell transduction of chemical signals, is likely to lead to specific tools which will aid drug discovery and development. Knowledge of molecular chaperones will enable the efficient manufacture of natural and unnatural multi-subunit proteins. Developments will extend beyond proteins to active RNA species which might, for example, provide novel therapies for viral

infections if they can be designed to operate inside cellular environments.

6.1.7 The production of cells with particular desirable characteristics raises even more intriguing prospects. For example, implantation of genetically engineered human cells might be used to treat deficiencies of hormones - insulin-secreting cells are already being considered for diabetes. Extension to neurotransmitters could have major benefits for certain forms of mental illness, and extension to growth factors and other products such as perhaps extracellular matrix might be used to promote tissue repair - even in the nervous system. Manipulation of the immune system as a whole by this approach and by controlling natural intercellular signalling mechanisms within it could lead to new treatments for infections and autoimmune diseases. Applied to plants and microbes, the extensive re-design of whole organisms could lead to chemicals and materials which are not available from existing natural resources.

6.2 Intermediate Value Chemicals

6.2.1 The drive to produce high value chemicals more cheaply has led to development of methods of increasing yields of product in microbial or human cells, and has brought production of intermediate value chemicals into sight. Such chemicals, e.g. intermediates in the synthesis of vitamins, drugs, pesticides, or colouring matters have traditionally been made by synthetic organic chemistry. Biotechnology offers some special advantages, particularly in the synthesis of chiral centres and is beginning to compete. The substances can be produced by enzymes in the living cell, for example the production of vitamin C in a modified micro-organism, or by isolated enzymes e.g. the production of high fructose syrup by glucose isomerase. Enzymes themselves may be products, e.g. in washing powders, and the proteolytic enzyme subtilysin, used in this way, has been modified extensively by

protein engineering (see appendix D).

6.2.2 By using microorganisms as biocatalysts the subject of biotransformations is offering potential to the chemical industry. Chemical processes produce isomer pairs in equal amounts, only one of which is biologically active. The other will be at best a harmless diluent, or at worst a toxic contaminant. It is likely that there will be increasing pressure on companies to remove biologically inactive isomers from their products. ICI have invested in a new plant to produce optical isomers of hydroxy alkanoic acids and the Japanese and Americans are known to be investing heavily in the area of biotransformations. A LINK programme in biotransformations was approved early in 1989.

6.2.3 The use of micro-organisms as biocatalysts also has potential for application in the food industry, for example in the production of antimicrobials for food preservation.

6.3 Production of Monoclonal Antibodies

6.3.1 This is now a well established technology and production of large amounts of highly specific pure antibodies are routine. These have been up to now, for technical reasons, mouse antibodies but the new technique of producing mouse-human hybrid molecules by protein engineering opens up important new applications.

6.3.2 The application of monoclonal antibodies for use in in-vivo imaging of targets or for targeting of drugs to tumours is of considerable medical potential.

6.3.3 An important recent development is the utilisation of simple expression systems, for example in bacteria, for the production of single domain antibodies. The ability of an animal to produce an antibody precisely tailored to any of the effectively infinite array of possible foreign molecules (pathogens) depends upon the

sequential application of three mechanisms. Firstly, each chain of the four chain antibody molecule is assembled from a number of segments. Secondly, each half of the symmetrical molecule is assembled from two such chains. Lastly, a process of random mutation can diversify the molecule still further. Together these mechanisms allow an animal to produce between 10^8 and 10^{10} different antibody molecules. The original discovery of monoclonal antibody technology allowed just one of this vast array of antibodies to be selected and expanded indefinitely. Two recent developments may lead to substantial improvements in the speed and accuracy of this technology. Both depend upon the expression of libraries of antibody genes in bacteria. The first advance, from Greg Winter's group at the MRC Laboratory of Molecular Biology, was the demonstration that a single chain of an antibody molecule could have significant specific binding activity. The initial diversity produced by this approach depends upon just the first of the mechanisms outlined above. The second development, from Richard Lerner's group in California, involved the combination of two libraries representing the two chains of an antibody; this effectively mimics the second mechanism and produces a library with an estimated 10^{12} different members. In both cases the libraries can be directly screened for members that bind to molecules of interest, and in principle the selected members could be subjected to controlled mutation to increase the binding specificity. These methods hold the promise of allowing the selection within days of highly specific monoclonal antibodies, a process which at present takes months and involves the uncertainty of the quality of the antibodies produced by an individual immunised animal.

6.4 Novel Plant Species : Plant Biotechnology

6.4.1 As well as being an essential component of all ecosystems, plants have been used by man for food, fuel, medicines, building materials and decoration. Over the centuries, beneficial and

useful plants have been bred to improve particular characteristics. Improvement depended on genetic diversity within species and relied on sexual crossing for the development of new varieties, although spontaneous mutants can sometimes arise. In general, production of new varieties through sexual crossing is a slow process, taking 10-20 years before a new variety enters agricultural production.

6.4.2 Increased development in the Third World is leading to the loss of the wild populations which have been the main source of genetic diversity for breeders. Steps have been taken to counter this through the establishment of gene banks but there is still concern that lack of germplasm could limit future development of improved varieties through traditional breeding.

6.4.3 Plant biotechnology offers an alternative route to developing new varieties by providing the means to genetically manipulate plants without the need for sexual crossing. It will be possible to introduce attributes from one species into another through direct gene transfer or by the fusion of protoplasts (cells from which the cell wall has been removed). While much needs to be done to bring this into practice, lack of genetic diversity within a species should not in future limit development of new varieties; desirable genetic attributes will simply be introduced from elsewhere, including from bacteria, fungi or animals. In addition, isolated genes may be modified and then reincorporated into the genome to produce proteins with new properties such as enhanced enzyme activity or increased nutritional value. The level of expression of genes can also be altered leading to an increased content of useful products (e.g. proteins, starch, oils, fibre or pharmaceuticals).

6.4.4 Substantial progress has recently been made in isolating, characterising, reconstructing and introducing genes into crops which confer properties such as resistance to herbicides, insects and viruses. It is possible to modify genes in the

micro-organisms that affect plant growth, e.g. of nitrogen fixing bacteria or more generally of the plant growth promoting micro-organisms.

6.4.5 Plant biotechnology offers considerable opportunities for plant improvement. These include (for more details see appendix B):

- better strains of trees for timber, food or other products eg. poplar, coffee, rubber, oil palm

- better strains of arable crops that require less fungicide, pesticide and fertiliser

- plants with improved stress tolerance (eg. chill, heat, drought, acid resistance)

- crops with improved nutritional quality

- crops with greater appeal to the consumer (eg. better quality, improved taste)

- crops with properties that can be used in new cost-effective ways as raw materials in industry.

6.5 Genetic Modification of Animal Genomes

6.5.1 Animal biotechnology is expected to have an impact on agriculture over the next few years and will be of importance to the European Community (EC). It is already possible to introduce foreign genes into animals - with observable physiological effects. The production of 'super mouse', a transgenic mouse with a human growth hormone gene, is a well known example. This approach is now being applied to production of high value chemicals, e.g. production of human Factor IX by sheep derived from fertilized eggs

injected with the appropriate foreign gene, followed by secretion into the milk. Animal biotechnology offers opportunities to improve:

- animal quality in terms of production performance or the expression of introduced foreign genes

- animal health with respect to disease resistance

- animal welfare

6.5.2 There will be considerable opportunities for animal biotechnology in animal health and husbandry, offering opportunities in growth and lactation, in-vitro fertilization and embryo transfer, diagnostics, vaccines and therapeutic drugs, and in feed additives. These aspects are discussed in more detail in appendix C. Animal cell biotechnology is an area for future exploitation. The expression of proteins in animal cells, and the growth of these in fermenters, could offer considerable commercial opportunities. The SERC and several UK companies are currently funding a joint research programme in this area. The use of transgenic animals to provide disease models offers substantial potential. Transgenic animals and embryonal stem cell biology are considered separately in appendices C.1 and C.2.

6.6 Detection of genetic variation in humans and the potential for future gene therapy

6.6.1 There are an estimated 4000 single gene defects, affecting about 2% of the population. Examples include cystic fibrosis, haemophilia, sickle cell anaemia, thalassaemia, Duchenne muscular dystrophy and some enzyme defects (eg. adenosine deaminase [ADA] deficiency).

6.6.2 Genes are also known to be important in the development of

some of the more common ailments such as cancer and cardiovascular disease. It is thought that these conditions involve both a number of genes and environmental factors - possession of the relevant genes providing susceptibility to disease rather than its certain development.

6.6.3 Considerable research efforts are being made to trace the gene or genes implicated in various diseases. The precise genetic variations responsible for sickle cell anaemia are known and that for cystic fibrosis has lately (September 1989) been found. Genetic markers have been discovered for a number of other genetic diseases.

6.6.4 The discovery of a gene defect or of genetic markers for a disease makes it possible to screen for that disease, or for susceptibility to that disease. Such genetic information provides the opportunity for future development of novel pharmacological or gene therapies. Gene therapy is actively being researched but is still some way from becoming a reality. The objective of present research is, having identified the abnormal gene or genes, to correct these abnormalities by insertion of normal genes.

6.6.5 There are two separate areas for potential gene therapy; somatic therapy and germline therapy. It is important to draw a distinction between the insertion of genes into somatic cells which will not produce inheritable alterations and the introduction of genes into the germline cells. In this latter case the genetic alterations would be inherited by all cells in all subsequent generations. Current approaches to human diseases are focused on introducing genes into somatic cells. The potential of both somatic and germline therapies are considerable (see Appendix A).

6.6.6 Current research in animal embryonal stem cell biology is leading to increased knowledge of the characteristics of stem cells in the developing embryo and in the adult. This work will underpin

the introduction of new techniques of medical treatment, including somatic gene therapy of genetic diseases. It could eventually lead to the establishment of cell engineering and the production of 'designer cells' with specific desirable functional properties, aimed at the prevention or cure of disease (see appendix C.2).

7. PRESENT ACTIVITIES IN BIOTECHNOLOGY

7.1 Introduction

7.1.1 Since the early 1970's a considerable number of biotechnology companies have been founded, mostly in the USA. Numbers and definitions vary; a survey of the US in mid-1988, by Arthur Young, included 1037 US biotechnology companies. This number includes suppliers to the industry but excludes major pharmaceutical firms or other well-established corporations.

7.1.2 The UN report on Transnational Corporations indicates that in Japan and W Germany the majority of biotechnology activity was in major corporations, unlike in the USA and most other OECD countries, where both new companies and established transnational corporations are involved. Of the 500 largest companies based in the USA and listed in 'Fortune', at least 10% were reported to have activities related to biotechnology in 1986. In the case of firms not based in the USA, of the 500 largest companies listed in 'Fortune', at least 62 had activities in biotechnology. Of these, 19 were based in the UK, 19 in Japan, and 6 in W Germany.

7.1.3 In the following sections we summarise the present level of research and commercial activity in Biotechnology, in both the UK and in major competitor countries.

7.2 United Kingdom

Company scene/level of industrial investment

7.2.1 Present industrial support for biotechnology in the UK follows three broad trends. These are;-

i) biotechnology activities within the major UK companies, mainly pharmaceutical and chemical companies, such as Beecham, Glaxo, ICI, Shell, Unilever and Wellcome.
ii) biotechnology companies such as; British Biotechnology Ltd., Celltech, Delta and Porton International (whose prime objectives are the discovery and development of new therapeutic entities); Animal Biotechnology Cambridge and the Agricultural Genetics Company (both of whom are involved in agricultural biotechnology).
iii) small companies set-up to exploit monoclonal technology, particularly in the field of clinical laboratory diagnosis.

7.2.2 The major UK chemical and pharmaceutical companies were more cautious in their investment in biotechnology than some of their competitors, especially US competitor companies. In the knowledge that many US biotechnology companies are still not operating at a profit, this reflects the reluctance of UK companies to act until they saw the real commercial targets. However, over the last couple of years many have considerably increased their investment in biotechnology.

7.2.3 Wellcome entered biotechnology at an early phase. They have made a significant contribution to mammalian cell methods for producing complex human therapeutic proteins. Glaxo's recent acquisition of Biogen in Switzerland now places them in a significant position in this technology. Beechams recent merger with SmithKline has greatly increased the available biotechnology in R&D, at SmithKline's Philadelphia facility.

7.2.4 ICI have integrated biotechnology into many of their bio-businesses. ICI entered the Seeds business with the acquisition of the Garst Seed Company in 1985. This was seen as a means for exploiting the potential for plant biotechnology and by further acquisitions ICI now have a major international seed company. Unilever have also moved into the seeds business by their purchase of part of the Plant Breeding Institute from the AFRC.

7.2.5 ICI pharmaceuticals made a commitment to biotechnology at the beginning of 1988 by establishing a department of about 100 staff. All the skills expected of a medium sized venture capital biotechnology company are in place (cloning, mutagenesis, gene synthesis, transgenesis etc.). These are now being applied across their major therapeutic areas.

7.2.6 Until the Spinks' Report in 1980, biotechnology in the UK lacked venture capital support. Celltech was established in 1980 and has pioneered the large scale culture of hybridoma cells that produce monoclonal antibodies. Only Genentech and Wellcome have comparable facilities and technology.

7.2.7 From its inception Celltech has had a policy of fostering close links with academia; a policy central to the company's scientific development. The early links were exemplified by the exclusive arrangement with the MRC in areas of recombinant DNA and hybridoma technologies. Although this exclusive relationship has been modified Celltech maintains good links with relevant scientists in the MRC: Intellectual Property Rights are now granted on a project by project basis.

7.2.8 The AFRC also established an exclusive agreement with the Agricultural Genetics Company (AGC) in 1983, giving AGC first refusal on certain plant biotechnology research.

7.2.9 Animal Biotechnology Cambridge (ABC) has recently been set-up, funded largely by venture capital, to exploit the improvements that biotechnology offers in animal husbandry and health. Their recent merger with Ovamass Embryos, a leading Eire animal biotechnology company places the expanded company in a good international position. They, and the US company Granada, now represent the two major contenders in this field, worldwide.

7.2.10 Data on the level of biotechnology R&D spend by UK industry are difficult to obtain because the larger companies do not separately identify biotechnology research.

Underlying science/research base

7.2.11 There is activity in the general area of biotechnology in most British Universities. Many have biological or medical departments that are involved in recombinant DNA or monoclonal technology but groups are often too small and lack strength in the critical interdisciplinary skills. The UK has particular strengths in some of the relevant areas such as protein structure determination, protein engineering, stem cell biology and biochemical engineering, in particular continuous fermentation and antibiotic fermentation. However, apart from basic virology, microbiology is weak in the UK and UK immunology no longer holds the preeminent position it enjoyed in the 1960's.

7.2.12 There is biotechnology activity and strength in some of the Research Council Institutes. The MRC supports a good deal of fundamental biology which underpins the range of research carried out by the Council. It has made outstanding contributions in molecular biology and continues to have major strengths in this field. However, despite the recent establishment of an IRC, cell biology in the research council supported units and institutes, and in university departments, needs further strengthening. The AFRC Institutes are important interdisciplinary research establishments

with particular strengths in the plant sciences, in microbial genetics, and in animal transgenics and animal physiology. The AFRC, in their corporate plan 1989-1994, have identified several areas relevant to biotechnology as priority areas for selective funding. These include; stem cells, molecular switching of gene expression, the release of genetically engineered organisms, and the molecular basis of food biotechnology and processing. The NERC Institute of Virology and Environmental Microbiology has programmes of research on genetic engineering and custom design of viral insecticides, on the molecular biology and genetic engineering of other microorganisms, and on plant viruses.

7.2.13 Biotechnology may be defined in different ways and hence an estimate of the expenditure by Government and the Research Councils is difficult to achieve. In the report 'The Biotechnology Directorate of the SERC' (SPRU, 1988) the following heavily qualified figures for 1985/86 are given; AFRC - £10.0M; MRC- £31.0M; NERC - £0.8M; SERC - £11.7M. More recent data on biotechnology spend has been provided to the Committee by the Research Councils as follows; AFRC - £25M (88/89), split £12M on animals, £11M on plants and £2M on food; MRC - £37.1M (87/88), split £35.9M on underpinning research and £1.2M on research with a clear intent; NERC - £5.5M (88/89); and SERC - £13.6 (88/89). Care is needed in interpreting this data. The SERC figure represents only their direct support of university/polytechnic research grants and studentships in biotechnology and does not include funding for research in the underpinning sciences nor in-house costs, building costs or UFC (University Funding Council) related costs. An approximate figure for the support of the biological sciences by the UGC (University Grants Committee; now replaced by the UFC) in 85/86 was £59.5M. The DTI spent about £5.5M on biotechnology in 1988.

7.2.14 In the period since the Spinks report industry/University collaboration has grown. The successful development of DNA

fingerprinting arose from cooperation between Leicester University and ICI. The links between British Biotechnology and Oxford University and Amersham and Birmingham University are proving successful. There are also several LINK programmes, as mentioned earlier, which offer prospects for future commercial developments stemming from University research. These include those in Eukaryotic Genetic Engineering, Biotransformations, Control of Plant Metabolism, Molecular Sensors and Biochemical Engineering. However, **despite the growth of industry's investment in biotechnology in British Universities the level remains small compared with US and Japanese company investment; an increase in such industrial support would greatly enhance the transfer of the scientific expertise into commercial success.**

Manpower levels/training implications

7.2.15 A UK Interest Group on Education in Biotechnology was formed in mid-1988 to liaise with the European Federation of Biotechnology (EFB). Following a meeting held in April 1989, a report by this group concluded that biotechnology, in relation to its manpower and training needs, is uniquely characterised by its recent and rapid commercialisation, its multidisciplinarity and pervasiveness, the high skill levels required by the industry and the limited transferability of skills between sectors. Serious concern was expressed at the future levels of manpower supply in biotechnology. Selective skill shortages in biotechnology were reported to have existed for a number of years, particularly in areas such as plant molecular biology, plant and tissue culture, microbial physiology and microbiology, enzyme technology and fermentation, and downstream processing and biochemical engineering.

7.2.16 A number of recommendations were made including: there should be increased funding for advanced level training and the research with which it forms an integral part; industry should take

a leading role in the training process; the SERC Teaching Company Scheme in biotechnology should be expanded and the Integrated Graduate Development Scheme should be extended to biotechnology; improved training should be provided in the area of identifying, protecting and exploiting intellectual property rights.

7.2.17 This Committee has heard strong and convincing evidence that the skill shortages represent the most serious potential limiting factor to the UK's ability to develop and exploit biotechnology. Since biotechnology depends on various disciplines, and has its roots in basic sciences such as genetics, microbiology, chemistry and physics, the long term solution to the present difficulties is likely only to be found in a broadly based improvement in the UK science base. The general and vitally important problem of skilled manpower shortages is the subject of a separate study by ACOST. Of the various issues to be addressed specific measures to enhance recruitment of PhD and postdoctoral workers in biotechnology should be considered urgently. The full exploitation of the potential improvements in health care requires a cadre of clinical research workers trained in molecular and cellular biology. **We recommend that the DES, the Research Councils, and the DTI urgently consider a coordinated approach with industry to ensure the provision of skilled manpower in biotechnology and its related industries.**

7.3 Japan

7.3.1 Japan has a long history in fermentation technology but interest in new biotechnology began to take shape in 1981 when MITI chose recombinant DNA technology, bioreactors, mass-cell culture and biochips as research topics in its Basic Technology for Future Industries R&D programme. In 1982 it set up a Bioindustry office aimed at identifying industrial opportunities to support the bio-industries. The Japan Key Technology Centre was set-up in 1985, offering loans and grants to private sector research institutes.

7.3.2 The present (1988/89) Japanese Government spend on biotechnology research is estimated to be £230M. MITI have recently been carrying out research in a number of areas including;

- recombinant DNA
- the development of fuel grade alcohol technology using bacteria
- new fuel oil technology using biomass and
- fine chemicals production technology.

7.3.3 In 1985 MITI initiated a six year project to develop a system for recycling contaminated water using biotechnology and membrane separation techniques. Earlier in 1989 it was instrumental in setting-up a joint public/private research centre to promote marine biotechnology.

7.3.4 A Protein Engineering Research Institute has been jointly funded by the Japanese government and a number of the major corporations including; Kyowa Hakko Kogyo, Mitsubishi Chemical Industries, Toa Nenryo Kogyo, Toray Industries and Takeda Chemical Industries.

7.3.5 According to a UN report on Transnational Corporations there are now some 150-200 Japanese companies active in the industrial development of biotechnology. Unlike the US and much of the EC, this is almost exclusively in the larger Japanese companies. Venture capital funding is only just beginning to increase in importance. Again data on the level of industrial expenditure are scarce, approximate and vary depending on the definitions used. The OECD have estimated that Japanese industry spent about £380M in 1985 on R&D in biotechnology.

7.4 The United States

7.4.1 The United States must be regarded as the world leader in the commercial exploitation of the biosciences. By far the largest number of biotechnology companies are based in the US. The 1987 US industrial expenditure on biotechnology R&D is estimated by the OECD at $1.4B. A US Office of Technology Assessment (OTA) report estimates federal support for biotechnology in 1986/87 at $2.5B, if a broad definition of biotechnology is taken; or $1.0B if a narrower definition is taken.

7.4.2 The two main federal support agencies for research related to biotechnology are the National Institute for Health (NIH) and the National Science Foundation (NSF). The NIH budget of over $6B is used to support basic biomedical research, some of which will be of benefit to US biotechnology. NSF support for biotechnologically related projects in 1987 amounted to over $107M, the majority of this being for underpinning research in microbial genetics and cell biology. The NSF have more recently established a biotechnology programme with priority attention to cell culture systems, bioreactor design, separation and purification processes and analytical monitoring methods.

7.4.3 Many individual States have also encouraged biotechnology research in order to stimulate local economies. Data from the Directory of States Biotechnology Centres, Mark Dibner, Feb 1988, identified 40 biotechnology centres with total funding of $83M in 1988, of which 60% is State money.

7.4.4 Over 60 US corporations have significant programmes in biotechnology and over 300 new biotechnology companies were founded in the US between 1980 and 1986. Over 1000 companies were assessed by Arthur Young in mid-1988 as having business related to biotechnology.

7.5 Europe

7.5.1 The first Community initiative in biotechnology was the Biomolecular Engineering Programme (BEP) from 1982-1986. This was replaced by the Biotechnology Action Programme (BAP) which was adopted by the Council of Ministers in March 1985 for the period 1985-1989. The budget for this programme was 75 MECU (about £50M) and included activities in research, training and concertation. Basic biotechnology research in the programme included enzyme engineering, genetic engineering applied to micro-organisms for industries, plant and soil micro-organics, and animal husbandry; methods of assessing risks associated with new biotechnology; and technology of cells and tissue cultured in vitro.

7.5.2 The Biotechnology Research for Innovation, Development and Growth in Europe (BRIDGE) programme (1990-1994; 100 MECU) will continue the work of BAP in strengthening the scientific base of Europe's biotechnology. The research activities will include information infrastructures (culture collections, data processing), enabling technologies (gene mapping, biotransformations, molecular modelling, etc.), cellular biology and pre-normative research (for example safety assessments and evaluation of toxicity).

7.5.3 Other recently proposed EC programmes relating to biotechnology are the European Collaborative Linkage of Agriculture and Industry through Research (ECLAIR) programme (1988-1993; 80 MECU); the Food-Linked Agro-Industrial Research (FLAIR) programme (1989-1993; 25 MECU); and the Agricultural Research Programme (1989-1993; 55 MECU).

7.5.4 In the Federal Republic of Germany the Ministry for Research and Technology (BMFT) provided DM 261M for genetic engineering in 1988, according to a recent BMFT press release. Several new 'gene centres' have been founded including those in Heidelburg, Berlin, Cologne and Munich. Other priority areas receiving BMFT funding

include bio-process technology (at Braunschweig, Gottingen, Hanover and Stuttgart) and molecular biology (at Hamburg). The total west German government spend on biotechnology was estimated by the Biotransformations Club (BTC) as £329M in 1987 (at 3 October 1989 exchange rates), although again it must be realised that there are difficulties in comparing figures due to the different definitions used.

7.5.5 With the same proviso about the difficulties in obtaining exact figures, the other major EC biotechnology research is carried out in France (£204M, 1989 figures from an Official French paper); Italy (£47.7M, average of a 5 year programme, biotransformations club [BTC]); Denmark (£16.6M, 1989 figure from an official Danish booklet); the Netherlands (£5.7M, average of a 5 year programme, BTC) and Spain (£5.4M, 1989 figures from a paper by the Concertation sub-group of EC Biotechnology Central Management and Advisory Committee) .

Appendix A

THE POSSIBLE IMPACT ON FUTURE DEVELOPMENTS IN BIOTECHNOLOGY OF NON-TECHNICAL FACTORS

INTRODUCTION

Biotechnology embraces a wide range of scientific and industrial disciplines. The term 'biotechnology' is usually understood by the general public as involving some form of genetic manipulation but this represents only a small proportion of all the activities presently classed as biotechnology. The OECD refer to a 'new biotechnology' which has evolved from recent developments such as genetic engineering and cell fusion. The importance that this new biotechnology will have in the 21st century is highlighted in their report entitled "The Economic and Wider Impacts of Biotechnology", to be published in 1989. Whilst admitting that it is difficult to analyze and measure 'quality-of-life' changes, the report states that;-

> 'the new biotechnology is distinguished from other major technologies of the 20th century by the fact that its impact on the quality of life, its human and social consequences, are arriving earlier and may go deeper than macro-economic impacts measured by productivity, investment or GDP growth'.

The benefits of biotechnology are widespread. New developments will lead to a better understanding of life and health and to the provision of new sources of biological drugs, vaccines and diagnostic reagents. Biotechnology will facilitate major developments, such as prevention and cure for AIDS, which would otherwise seem to be unachievable. There will be advantages in agriculture and food production, for example in the breeding of

plants which are more resistant to pests and viruses, or in the production of food with improved quality and nutritional content. Plant biotechnology will contribute to environmental improvements and also provide major opportunities for increased food production in the third world.

The social and moral implications of some of these developments are considerable. As with all forms of technological advancement new biotechnology will have profound socio-economic consequences, distinct from safety and ethics, which will need to be addressed. These include the continued development of second and third world countries and the survival of small farmers. The possibility of modifying the genetic make-up of organisms raises many questions in relation to the 'manipulation of life itself'. There are complex issues associated with particular innovations such as the use of genetic fingerprinting, work on sequencing the human genome and the possible future use of gene therapy (somatic and germline). The potential impact that genetically modified organisms may have, for example, on the environment or the food chain leads to discussion on the safe use of these techniques. A common concern is the fear of the release of 'superbugs' which may generate worldwide disease or ecological disaster. These and other aspects appear to indicate that biotechnology will affect man and his social relations more directly than has so far occurred in any technological development.

The social and regulatory implications have unfolded steadily in parallel with realistic applications of the technology. Debate on potential benefits and associated risks began at an early stage in the growth of biotechnology and has already shaped its progress to some extent.

The impact of biotechnology will be pervasive. Public perception, and governmental response, will be of paramount importance in setting a regulatory framework and determining the rate and direction of the diffusion of the technology. The power of public

feeling must not be underestimated; consumer resistance and fears for safety and pollution, for example, can seriously encumber commercial prospects. Recent public fears over toxic PCB (polychlorinated biphenyl) waste and consumer resistance to food irradiation are examples of this point. Technically, food irradiation has been possible for over twenty years but negative consumer reactions have effectively prevented its use in the UK until recently.

Present concerns over biotechnology are confused, giving rise to the danger that adverse public perception will be mis-directed. Some concerns are related to safety, others are founded on serious ethical issues arising from particular developments, but numerous worries originate from 'a fear of the unknown'. Many products of the new biotechnology are no different, in principle, from the products of plant and animal breeding that have been accepted for centuries. However, the speed of these advances, and the fact that it is now possible to accomplish certain things that were previously impossible, such as the production of human factor IX in sheep, increases the fears that scientists are perpetrating something 'unnatural'. It is also possible to argue that some aspects of biotechnology provide a more 'natural' process or product for example, by allowing for the reduced use of fertilizers and chemicals in agriculture. It is not possible to deal with such a diverse range of issues in a global manner and it will be important, therefore, to clearly distinguish the following broad areas of biotechnology;

- those that have safety implications
- those where safety and ethical issues need to be considered in parallel and
- those where there are few or no new worries.

In the following sections we consider how these various non-technical factors may influence future progress in biotechnology.

On the whole they represent potential rate-limiting aspects to the development of the technology and we make a number of recommendations as to how these may be overcome.

SAFETY ASPECTS

The safety of the worker, the consumer and of third parties are each of major concern. Regulations are now emerging along three principal lines; worker safety, product safety and protection of the environment (discussed separately).

Concerns regarding developments in biotechnology became evident in the late 1970's. Discussion at that time was dominated by the question of health hazards to laboratory and industrial workers or people in the local environment. An example where worker protection is essential is in the research and development of vaccines against infectious agents. However, once genetically engineered vaccines are produced there is no risk of contagion as the use of the organism itself is circumvented.

Initially, regulation of biotechnology in the UK stemmed from the work of the Genetic Manipulation Advisory Group (GMAG). This Group, reporting to the DES, produced a series of advisory notes aimed at controlling the practice of the technology at the laboratory level. Subsequently the Advisory Committee on Genetic Manipulation (ACGM) was set-up, reporting to the Health and Safety Executive (HSE). Revised guidelines have recently been prepared which also cover new scientific and technical developments such as work on transgenic animals and work on cloned oncogenes. The scale-up of industrial processes based on recombinant DNA technology are also included in these new guidelines. The possible risks of using viral vectors for human therapy are presently being assessed jointly by the ACGM and the Advisory Committee on Dangerous Pathogens.

The consensus view in the area of worker protection and safe contained-use is that the UK has reached a position which optimises all aspects of safety without imposing unnecessary constraints which do nothing for worker safety. The ACGM has been very successful in dealing with the interface between the science and the public perception in this area, recognising the importance of early dissemination of information to the media, and this has largely averted the outbreak of sensationalist journalism. The ACGM has gained a worldwide reputation for its work and its approach has been used as a model by many other countries.

The parallel introduction of regulations and guidelines in the US has had a more checkered path. Public outcry at an early stage caused considerable difficulties. However, some comparison can be drawn between the current position in the US and that of the UK, on the basis that the National Institute of Health (NIH) guidelines differ from those in the UK only in minor detail.

With regard to pharmaceutical product development in the EC, USA and Japan product safety issues are dealt with within the framework established for synthetic medicinals. The only exception relates to products potentially containing live organisms, such as vaccines. The differences are accommodated by guidelines on the assessment of product quality, safety and efficacy.

A number of EC regulatory initiatives in biotechnology are planned at the present time. There is, however, some industrial worry about the direction being taken by the EC in these since most discriminate against a product because genetic manipulation has been used at some stage in its manufacture. The OECD, and other independent international groups, contend that it is the product which should be evaluated for risk, and not the means used to produce it. **The UK government should press for this view to predominate in discussions in the EC.**

The production of foods derived from, or composed of, manipulated microorganisms is another area of potential concern. The Ministry of Agriculture, Food and Fisheries (MAFF) has recently set-up an Advisory Committee on Novel Foods and Processes (ACNFP) to provide advice on the safety aspects of such food. A serious impediment to development may result from food pressure groups who argue that these processes are 'unnatural' and should not be used. Consumers have already expressed doubts about the safety of milk produced from dairy cows injected with the genetically engineered protein bovine somatotropin (bST), although there is no evidence that it is harmful to human health (nor is there any reason to believe that milk produced from a cow injected with bST could be any different from 'normal' milk). Consumer reaction could well be mobilised against developments in the food area but MAFF are presently taking a cautious approach in respect of changing attitudes towards food. **MAFF and its Advisory Committee on Novel Foods and Processes must take a more proactive role. We recommend that MAFF consider appointing a consumer representative to the ACNFP.**

The outcome of present negotiations for the licensing of bST in the EC could set the tone for years to come for the introduction of biotechnological products in the European market. If approved bST will be the first genetically engineered product licensed in Europe for agricultural markets. However, calls for a moratorium to allow for further scientific study have been strong, as have the views of a range of consumers, environmentalists, farmers, industrialists and politicians (both American and European). It has now been announced that there will be an evaluation period up until the end of 1990. A number of US pharmaceutical companies have invested a considerable sum of money into the production of genetically-engineered bST and are anxious to see the product licensed. The US might see a European moratorium as a non-tariff trade barrier.

The UK is well represented on Committees involved in the development of EC regulations, and it will be important for the UK

to continue to have a strong voice in the EC in what will inevitably be a high profile political topic.

ENVIRONMENTAL ASPECTS

The introduction of genetically engineered organisms into the environment is a contentious subject. In the UK and France there has been to date very little public criticism (and probably concern) about introductions. In the UK this is possibly because the HSE were quick to establish a sub-committee of ACGM to produce guidelines and subsequently regulate such introductions. This committee has been careful to use a definition of 'genetic engineering' that is sufficiently broad to cover all types of novel organisms that may give rise to concern; a good example of this is the release of a strain of an agriculturally-important microorganism (Rhizobium) which occurred in France, Germany and the UK in 1987. The UK committee decided that the organism had been manipulated and vetted the release. Neither France nor Germany made an assessment; in both countries there was considerable criticism of the scientists and regulatory bodies, whereas in the UK there was no public concern, nor debate.

The current situation in Europe is that introductions are assessed by committees in France and the UK, and are allowed to proceed with the minimum of delay. In Denmark there is a law preventing releases without formal approval, and in Germany there is intense public pressure to prevent releases. Public opinion in Germany is being mobilized most efficiently to restrict all forms of use of manipulated organisms, whether they are contained in industrial plants or not. This could provide the UK with some commercial advantage because it seems very unlikely that any German pharmaceutical company (or any other company) will be able to exploit genetic engineering within the Federal Republic. However, any advantage here may be short-lived if German pressure in

Brussels leads to stringent EC regulations for the exploitation of genetic engineering. Were this to occur, Europe would be at a serious disadvantage in comparison to the USA, which is now fairly well organised and is approving many introductions (approximately 25 in 1988).

However, at a meeting of Environment Ministers in September 1989, a political agreement was reached on the content of an EC Directive on deliberate release. Further stages are needed before being finally settled, probably in 1990. The broad structure of regulation that is likely is that those wishing to undertake releases to the environment for purposes of research and development will be required to notify a national competent authority. The authority must respond within 90 days. An information exchange system, between national competent authorities, will be operated but the final decision is taken on a national basis. There is the possibility of developing simplified procedures, as experience develops.

The DoE published in June 1989 a Green Paper on the release of Genetically Manipulated Organisms. Proposals included replacing the present voluntary guidelines with a legal duty for researchers to notify the Department and to obtain its consent before releasing genetically engineered organisms. A new Inspectorate, under DoE control was proposed to monitor and enforce these regulations. Responses to this consultative paper are presently being coordinated by the DoE.

The Royal Commission on Environmental Pollution (RCEP) published a report in July 1989 entitled 'The Release of Genetically Engineered Organisms to the Environment'. Members of the Commission accepted the argument that too little is known of the possible risks of releases and that it is necessary to proceed in a cautious manner. New legislation is proposed to back up a system of compulsory registration and licensing for any release of genetically

engineered organisms and it is recommended that the release of an organism without a license should be made a criminal offence. The report says that the releasers must be required not only to monitor and report their results for the agreed duration of the experiment, but to continue monitoring for 'an appropriate period' thereafter, with a degree of imagination in order to catch any unexpected signs of damage.

The RCEP praises the work of the Intentional Introduction sub-committee of the ACGM and recommends that this Committee should be constituted in its own right to advise the Secretary of State for the Environment and the Health and Safety Commission on each proposed release. Further functions proposed for the Committee include: the development of codes of practice and guidance for applicants; to advise on the need for research and the possibility of categorizing releases; the review of the outcome of releases; to advise on the possible needs for changes in legislation or procedures and the production of an annual report.

The Royal Commission report also says that public access to information on releases is essential. There should be a public register of applications for release and product licences, and of licences granted. Public advertisement of proposed releases should be made to give members of the public the opportunity to make representations to the licensing authorities and access should then be provided to the information on which the expert committee has made their recommendations.

We endorse this cautious approach by the RCEP and **we recommend that the Department of the Environment quickly act on these recommendations in preparing new legislation for the release of genetically engineered organisms.** However, no consideration has been given to lay representation on the expert committee. Therefore, **we further recommend that DoE consider ways of providing for lay representation in these decision processes.**

Furthermore, we support the RCEP proposal for a reconstituted Committee within the HSE which will have the responsibility for advising the Secretary of State for the Environment on each release. This should be the one point where applicants seek permission to release and should not be duplicated by having a separate Committee within DoE.

While considerable attention is presently being paid to the environmental risks, there are also extensive environmental advantages to be gained from developments in biotechnology. Plant biotechnology is well advanced towards producing plants with resistances to insects and viruses. Their entry into agriculture over the coming years could result in reduced use of pesticides and other chemicals which affect the environment. Additionally, the production of chemicals safer to the environment will be possible. More distant, but of great importance to the environment, will be the identification of the genes responsible for nutrient efficiency and their utilisation in the major crop plants, allowing fertilizer usage to be decreased. **We recommend that the DoE fully consider the applications of biotechnology to the environment, including the beneficial aspects, and to convey the results of their assessments to the public.**

ETHICAL ASPECTS

It is an obligation for scientists to bear in mind the wider implications of their work. However, it is clear that the issues cannot be left to scientists alone and that society as a whole must provide ethical guidance which unambiguously defines the boundaries to what it regards as acceptable.

Issues such as the antenatal diagnosis of genetic disease, the development of analytical procedures to indicate susceptibility to disease, or the development of genetic probes that reveal

biological kin relationships with unprecedented accuracy (genetic fingerprinting) raise moral questions about how the data will be used. When the insurance industry begins to take more interest in genetic data considerable controversy will be likely. For example, the long term prediction of individual risk to specific diseases could be used to determine insurance premiums.

The discovery of the genes responsible for genetic disease will be considerably aided by the programme to map and sequence the human genome. This will lead to a better understanding of the mechanisms of disease and to the potential for genetic therapy through the modification of defective genes in vivo. This capacity to transfer genes between individuals arouses much public concern and fear. However, the very significant differences between somatic cell therapy and germ line therapy are often not fully appreciated. Somatic therapy offers considerable potential for treating debilitating, and often fatal, defects for which there are presently no cures. There will be little ethical difference between this type of therapy and other conventional types of therapy or organ and tissue transplantation. Germ line therapy, however, would affect the mix of genes in the general population and conjures up images of controlling human evolution and of crossing species barriers. A joint statement was issued in 1988 by the European Medical Research Councils in which it was recommended that germ line therapy should not be contemplated. Whilst this Committee appreciate these concerns it is also recognised that this then removes the option for the affected individual to chose to correct the genetic defect in subsequent generations; which then raises further moral issues. It was also agreed by the European Medical Research Councils that the application of gene therapy for the enhancement of general human characteristics raises profound ethical problems and it was also a recommendation that this should not be contemplated.

Many people feel an instinctive opposition to what they see as

'tampering with life', in particular human life. Public concern mounted following the birth in 1978 of Louise Brown, the first baby born as a result of in vitro fertilization (IVF). As a result of this a Committee of Inquiry into Human Fertilization and Embryology was appointed in 1982, chaired by Dame Mary Warnock, with the following terms of reference:

> 'to consider recent and potential developments in medicine and science related to human fertilization and embryology; to consider what policies and safeguards should be applied, including consideration of the social, ethical and legal implications of these developments; and to make recommendations.'

Amongst the issues raised during the inquiry were the moral and religious implications of embryo research. Many people were particularly concerned about the ramifications of possible future developments and the Warnock Committee discussed various possibilities (some purely speculative) including; ectogenesis (maintaining an embryo in vitro for progressively longer periods), the use of human embryos for testing drugs, cloning and techniques aimed at modifying the genetic constitution of an embryo. The recommendations contained in the Warnock Report, published in 1984, provoked considerable public debate. Continued consultation has occurred on these complex issues and Parliamentary Counsel have prepared a bill for this Parliamentary session. The bill offers alternative clauses, permitting research on the human embryo up to 14 days or prohibiting it altogether. The Government has agreed to allow a free vote on the issue.

The number of people with deep religious objections to gene cloning seems relatively small in Europe. Some religious debate has occurred over the last few years; a report by the Home division of the Methodist Church in 1981 considered aspects of technical change, including genetic engineering, and more recent reports by

the General Synod of the Church of England, 1985 and the Congregation of the Doctrine of the Faith (Vatican City), 1987 have been prepared following debate on human embryo research.

There is a shift of opinion, evident in some European countries and in North America, which maintains that animals have rights and that these are unacceptably violated by their use in agriculture, industry and research. The associated sentiments take many forms ranging from a vague sense that 'natural' cosmetics are preferable, to an intense antipathy towards any research or commerce that involves the use of animals. Most research institutes are fully aware of the problems that 'animal rights' groups can cause. The depth of feeling that results in attacks on buildings and individuals should not be underestimated. In Germany such feelings have even been aroused by plant manipulation experiments that are considered to be 'the thin edge of the wedge'.

Special issues will continue to arise due to advances in specific areas of biotechnology. At present the media, by their sudden highlighting of problems, cause the polarization of views among lay public and scientific communities, often on the basis of inadequate data. It is therefore important for government to become more proactive rather than perpetuating the need to establish ad hoc committees of inquiry. In order to deal with these many complex ethical issues **we recommend that government departments need to be sufficiently alert to the ethical issues that are likely to cause concern in the future.** We are aware that certain countries, such as Sweden and France, have established Ethics Committees but it is not clear how successful these have been to date. **We recommend that consideration be given as to how a detailed and systematic analysis of these, and other, ethical concerns can be carried out before public worries highlight particular issues. This should be on a case-by-case analysis, preferably by ad hoc Committees. The preparation of reliable independent information and analysis should form a part of this.**

Another vocal grouping, particularly in Germany, is one that rejects technology and anything that will benefit industry. As we know to our cost in the UK there is a deep-seated mistrust of fostering industry and these sentiments could have an important bearing on future developments.

WELFARE ASPECTS

Most examples of genetic engineering involving animals which are currently discussed by the press involve growth promotion, either through the use of growth hormone genes or bovine somatotropin. Photographs of an arthritic pig in the USA which was suffering because it carried a cloned growth hormone gene, has done considerable harm to the perception of the technology. The major advances that are occurring in the development of vaccines which aim to reduce disease and hence improve animal welfare are being less well reported. **The Ministry of Agriculture Fisheries and Food should consider how to convey better to the public the advantages offered by genetic engineering for the improvement of animal welfare.**

It is essential that the welfare of manipulated animals receives the highest priority at all times. We consider that these points are in general adequately provided for under the existing Animals (Scientific Procedures) Act, 1986, administered by the Home Office. The recently published ACGM's 'guidelines on work with Transgenic Animals' makes it clear that breeding from transgenic animals is a regulated procedure under the Animals (Scientific Procedures) Act. **We recommend that the Committees set-up to consider all license applications for animal experiments are kept fully informed of relevant issues that arise from developments in biotechnology, and that the welfare aspects of transgenic animals and their progeny are given careful consideration.**

SUMMARY

The impact that new biotechnology will have on society is immense. There are complex issues facing mankind where biotechnology offers the only realistic solution. The potential benefits are substantial and include the prevention of infectious diseases, cures for cancer and AIDS, improvement of the environment or the production of cheap and desirable food. All these will drive applications in biotechnology forward. Nevertheless, there are also risks associated with aspects of the technology and we have highlighted in this appendix how these may influence the rate of progress.

The many areas of biotechnology which do not give rise to new problems must be allowed to progress without hindrance. It is therefore essential for risk analyses to be carried out on a case-by-case basis. It is also important to ensure that there is the maximum of accurate public disclosure of projects and ideas; only in this way will people be in a position to make a reasonable judgement of the benefits and disadvantages, as well as make an ethical consideration of the issue.

Industry and government alike need to consider carefully the promotion of full public involvement in all aspects of the debate on biotechnology. Careful use of terminology is needed in the discussion of biotechnology with the general public, and in order to allow for an informed debate it will be essential to provide a balanced, non-commercial programme of education for the public on all aspects of the new biotechnology. **We recommend that government provides a programme of balanced information to the public on biotechnology.** Specific aspects could be dealt with by appropriate Departments, possibly with the Interdepartmental Committee on Biotechnology (ICBT) taking a coordinating role. As a part of this programme, **we further recommend that government consider the sponsorship of an independent body (eg. the Royal Society,**

Nuffield Foundation or the Leverhulme Trust) to produce a booklet providing the public with reliable information and analysis on these complex issues.

Appendix B

PLANT BIOTECHNOLOGY

INTRODUCTION

Plants are vital to the survival of the planet. Their importance includes the generation of oxygen and absorption of carbon dioxide and the provision of food. The development and management of plant resources is an essential issue for population stability. For developing and developed nations alike there are examples where agricultural practices with plants have led to soil erosion, over use of fertilisers, insecticides or pesticides or the general misuse of land. Plant Biotechnology will offer opportunities for better environmental options and will benefit both the food processor, with crops tailored to his processing needs, and the consumer, by providing better quality food in terms of texture and flavour.

The UK has many industries whose activities involve plant biotechnology. When integrated into the established practices of plant breeding and industry plant biotechnology can improve plants for UK profit by providing, for example:

a. better strains of trees for timber, food or other products e.g. poplar, coffee, rubber, oil palm

b. better strains of arable crops that require less fungicide, pesticide and fertiliser

c. crops with properties that can be used in new cost-effective ways as raw materials in industry.

In common with other areas of biotechnology, plant biotechnology has depended heavily on developments in molecular genetics and

genetic engineering of microorganisms. New opportunities within plant biotechnology have emerged due to dramatic progress in three broad areas:

a. improved methods for isolating plant genes (eg. 'transposon tagging'), determining their structure, modifying existing genes and designing new ones.

b. the development of methods for transferring genes to plants of potential importance in agriculture and horticulture. These include the introduction of DNA to plant cells, regulating their expression and achieving the regeneration of whole plants through tissue culture

c. improved understanding about the physiology, biochemistry, molecular biology and development of plants in order to exploit (a) and (b) above.

The UK was one of the first countries in the world to initiate the purification of plant genes by recombinant DNA techniques. The Plant Breeding Institute at Cambridge was cloning genes from the chloroplast genome in 1977. In 1978 the Agricultural Research Council launched a Plant Genetic Manipulation Programme. The genetic engineering of plants by molecular biologists was established in 1983. In that year, three programmes, one at the Plant Breeding Institute in the UK, produced tobacco plants containing an active gene that was constructed in the laboratory. This active gene conferred on the plant cells resistance to the antibiotic kanamycin and has been used extensively since as a means of selecting transformed plant cells in culture.

Since then, over 20 different species have been modified around the world by the introduction of new genes (none of these have occurred first in the UK).

Progress depends not only on the method of introducing DNA into plant cells but also on recovering whole plants from these cells. This aspect of plant tissue culture has limited the extension of gene introduction into other species. Potato, soybean and sugar beet have been transformed and in the last few months this has also been accomplished for rice and maize and is now almost achieved for wheat and barley. These latter four species represent approximately 60% of the total crops grown worldwide. Hence the commercial potential for new strains with novel or agronomically-useful characteristics is enormous.

The genetic and molecular basis for processes that are responsible for many desirable attributes in plants are not yet understood. Examples are factors affecting the composition of crops (e.g. fibre or oil content), the biochemical basis of growth in stressful environments, and the limitations to the efficient use of nutrients. All are areas where plant biotechnology could make substantial improvements to crops but more biochemical and physiological information is needed if molecular biological approaches are to have their full impact. This is particularly true when the desired improvements will require manipulation of plant-specific genes and useful properties cannot be imported from bacteria, fungi or animals.

A major area where lack of basic biochemical and physiological information is likely to limit progress is understanding of transport processes in plant cells. These are responsible for the uptake, internal redistribution, and final concentration of many compounds in plant cells. They play major roles in determining the composition of harvested produce, the responses of plants to external stimuli, uptake of agrochemicals, and in adaptation to stressful environments. Increasing the concentration of commercially-important compounds such as sucrose or pharmaceuticals in plant cells will require manipulation of these transport systems. In particular, the control mechanisms which limit the concentrations of compounds in cells will have to be overcome. At

this time, however, while the transport processes and control phenomena are recognised and described at the physiological level, their biochemical and molecular basis remains obscure in most cases.

PRESENT DEVELOPMENTS IN TECHNIQUES TO INTRODUCE NEW GENES INTO PLANTS

DNA can be introduced into plant cells by several means. When the cell wall is removed and protoplasts are produced, DNA can be introduced very easily by disrupting the membranes, chemically or by electric pulses. Such DNA can find its way to the nucleus and be incorporated into the chromosomes. In some species, the protoplasts can regenerate a wall, divide to form a callus and be induced to differentiate into a whole plant.

Many plant species are susceptible to the pathogenic bacterium Agrobacterium Tumefaciens. This bacterium causes crown gall tumours by transferring a specific segment of one of its plasmids into the chromosomes of plant cells and this has been exploited as a useful means of introducing genes into plants by replacing the bacterial genes in the special plasmid segment causing the tumour with genes of particular value.

Microinjection of DNA into embryo cells has successfully been achieved in oilseed rape. The shooting of a DNA-coated tungsten particle through cell walls and cell layers to transform cells has caused recent interest. A 'transfection gun' (Biolistic gene gun) is now on sale from Du Pont using this technique, which is based on development work at Cornell University. Cellular activity of genes shot into maize, onion, wheat, rice and soybean cells has been reported in the USA. Also, a DNA-coated gold particle, accelerated using electric discharge, has been reported to have produced transformed plants when fired into the meristems of immature soybean seeds.

GENETICALLY ENGINEERED PLANTS

It is estimated that there are as many as 40,000 plant genes and although a number have now been isolated, including ones that specify major seed proteins and enzymes involved in photosynthesis, in flower pigment production, in defence mechanisms and in the metabolism of nitrate and ammonia, there are many commercially important genes yet to be isolated. The method of 'transposon tagging' combined with 'restriction fragment polymorphism mapping' and DNA sequencing offers an important new approach to the isolation of useful genes. By determining the DNA sequence of these genes and by inserting a modified gene into the plant chromosomes, plants with completely novel properties are being created. This technology is well established in the UK and is the basis for an enormous range of commercial opportunities.

Substantial progress has been made in a relatively short time in isolating, characterising, reconstructing and introducing genes into crop plants which confer properties of direct agricultural interest, such as herbicide resistance, insect resistance and virus resistance.

Herbicide Resistance

Considerable progress in the engineering of selective herbicide resistance has occurred over the past few years because knowledge of the mode of action of the herbicides enabled target genes to be identified rapidly. The Monsanto herbicide, Roundup, inhibits the shikimate pathway enzyme, 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS) involved in aromatic amino acid biosynthesis. A mutant petunia gene was isolated by the Monsanto team which encodes an EPSPS protein that still retains its enzymic activity but is 6000 fold less sensitive to glyphosate inhibition than the wild type petunia EPSPS. When this gene, given a strong activating signal was inserted into tobacco and tomato plants it conferred

resistance to high levels of Roundup. Recent field trials of the tomato plants confirmed that resistance is inherited and does not have deleterious side affects on yield.

The Sulphonylurea herbicides of Dupont and also the imidazolinone herbicides of American Cyanamid inhibit the enzyme acetolactate synthase (ALS) which catalyses a step in the biosynthetic pathway of isoleucine, leucine and valine. Plants resistant to these herbicides have mutant ALS genes. Insertion of such genes from tobacco and Arabidopsis into tobacco or tomato plants by the Dupont team has produced plants resistant to high levels of sulphonylurea herbicides. Field tests in the USA have confirmed the value of the phenotype under agricultural conditions.

The antibiotic bialophos is a product of Streptomyces and can be used as a herbicide. Bialophos is produced commercially from Streptomyces while an analog, PPT, is synthesised commercially (Basta, Hoechst A.G). The Streptomyces gene which confers resistance to bialophos has been isolated, put under the control of a strong activating signal for plant cells, and introduced into a range of plant species in the company Plant Genetic Systems in Belgium. The gene product makes the plants resistant to high levels of the herbicide.

The rapid progress in this area reflect the large investment from the agrochemical companies who produce the herbicides. Their motivation has been in linking sales of their herbicides to that of crops resistant to it.

Insect resistance

The larvae of several major insect pests are controlled in agriculture in some countries by the spraying of spore preparations of the bacterium Bacillus thuringiensis. The insecticidal activity is due to crystals containing toxins in the spores. The genes encoding these toxic proteins have been isolated from many

different strains, put under the control of plant gene activating signals and inserted into various plant species. Some of the plants produced express the protein in their leaves to levels, which, when the leaves are eaten, cause the death of larvae. Death occurs within a few days and leaf damage is thereby highly restricted. In field trials carried out by Mansanto (USA) under conditions where control tomato plants were completely defoliated by tobacco hornworm, transgenic tomato plants suffered little agronomic damage.

A different gene has been used to confer insect resistance on plants by the group in the Botany Department at the University of Durham, supported by the Agricultural Genetics Company (Cambridge). They recognised that the level of a trypsin inhibitor, a naturally occurring protein in seeds of cowpea correlated with field resistance to the bruchid beetle. The gene for this protein was isolated, given a strong plant activating signal and transferred into tobacco. The gene product, expressed in the leaves, caused the death of larvae and thereby considerably reduced leaf damage. The cowpea trypsin inhibitor is apparently not toxic to humans so it may provide a useful route for protecting many plants used as human foods against insect devastation.

Virus resistance

A remarkable series of plants has been created recently by introducing active copies of genes encoding the coat protein of pathogenic viruses. The plants show considerable resistance to the viruses from which the coat protein genes were obtained. In a field test of transgenic tomatoes containing the coat protein gene of a common strain of tobacco mosaic virus, no more than 5% of the plants inoculated with TMV showed systemic disease symptoms compared with 99% of the control plants.

Another route to creating virus resistance tolerant plants by inserting viral genes is possible where the viruses have additional

small RNA molecules or satellites in their genomes. Viruses with satellites can sometimes be used to protect plants against more virulent strains lacking a satellite.

At the AFRC Plant Breeding Institute at Cambridge, in collaboration with the AFRC Scottish Crops Research Institute, a dimeric copy of a cucumber mosaic virus (CMV) satellite has been introduced into tobacco plants such that the gene was expressed as an RNA. Upon infection with CMV, the RNA was recognised, amplified and interacted somehow with the virus to reduce markedly the severity of the infection.

Improvements in plant breeding

Plant breeding is a laborious and expensive process. New methods in molecular biology are providing improvements in efficiency by allowing the presence of specific genes to be inferred and thus avoid assay for a complex phenotype in the field. Short segments of DNA are isolated from plant chromosomes and then used subsequently to make the particular region of chromosome from which they were isolated. Differences in that chromosome region between different plants can be detected and so breeders can infer which particular region and its associated genes is present in any single plant.

This approach has the potential to make major contributions to plant breeding practice and the assay of genetic variation, especially if the technology can be automated and reduced in cost.

The major UK companies already in plant breeding have recognised this and are now investing substantially in the production of sets of DNA probes which can be used to characterise genetical variation in all regions of the genomes of the major crop species. A consortium of companies has recently been formed by the Agricultural Genetics Company to fund such research for wheat in the AFRC Institute of Plant Science Research at Cambridge.

This is a major new development of the application of molecular biology to plant breeding and has been very catalytic in increasing the interest of plant breeders in the potential of molecular biology for plant breeding. These methods have already demonstrated their value in seed purity determinations and in proving the ownership of germplasm in courts of law.

Other opportunities for plant breeders and related industries are emerging from molecular biology. For example, kits to screen for the presence of pathogens, relying on detection of the foreign nucleic acids or pathogen proteins, have already been incorporated into plant breeding programmes and quarantine laboratories.

RESEARCH OPPORTUNITIES AND POTENTIAL FOR COMMERCIAL EXPLOITATION

To date, the limitations to the widespread application of plant biotechnology have been methodological. Techniques have had to be developed for isolating genes, studying and modifying gene structure and function, introducing DNA into cells, monitoring its expression, fusing plant protoplasts to produce intraspecies hybrids, and for regenerating whole plants from transformed cells. Although barriers still exist to the application of the techniques to all species of commercial interest, the major hurdles are being overcome. **More emphasis should now be placed on stimulating the utilisation of this research in order to isolate and manipulate the genes of key industrial potential and to learn how to manipulate them in plants of economic and scientific importance.**

We identify the following as major research opportunities in plant biotechnology with the potential for commercial exploitation:-

1. Development of methods to determine more precisely how gene expression is regulated during plant development,

leading to a better understanding of the developmental regulation of genes involved in processes such as flowering, tuber formation, ripening and senescence. This will permit the manipulation of plant properties and the control of protein synthesis leading to the following commercial possibilities:

- the improvement of the nutritional quality of crops by engineering the synthesis of proteins with different amino acids into the harvested parts
- plants with improved stress tolerance such as chill resistance, heat, drought and salinity tolerance and more tolerance to acid or high levels of heavy metals

2. improved manipulation of genes that determine the formation, size and shape of plant organs. This will provide more information about the molecular basis of plant development and will enable plants with novel growth habits to be created. Examples include:
   - the engineering of the male parts of flowers to prevent pollen formation. This will ensure cross-pollination and hybrid seed production in crops where this is desirable but not possible at present. Hybrid seeds often have added vigour and can give the seed producer extra protection against the use of the seed by a competitor.
   - the manipulation of the shape (and colour, see 4) of ornamental flowers and
   - the production of plants with improved storage of their harvested parts (eg.seeds) to avoid wastage and product deterioration

3. Improved understanding of nutrient efficiency, and identification of the genes involved, will permit the transfer to major crop plants, allowing fertilizer usage

to be decreased. This could have a major impact on environmental pollution.

4. The use of new techniques to better understand the genetic and metabolic control of biochemical pathways, leading to the development of ways to manipulate them. Important pathways include photosynthesis, those leading to the major harvested products of starch, oil and protein, and those involved in flower pigment production.

5. improved understanding of the mechanisms of pest and disease (including fungal and bacterial) resistance, leading to isolation and exploitation of the genes involved. These advances will increase plant yield and decrease the use of damaging fungicides, insecticides and pesticides. The major seed companies are now starting to invest in genetic engineering and some agrochemical companies have recognised the opportunity that biotechnology offers, to create novel plant characteristics and to produce a quality seed business, and have diversified into seeds.

6. The development of efficient procedures of putting genes into more plant species of fundamental and industrial importance such as the cereals and the legumes.

7. Plant cells change their behaviour in response to external, signals. (e.g. light, temperature, chemicals, water). How these signals are perceived and how they cause new internal responses need to be understood. This is an important area, especially to be able to manipulate plant behaviour using externally supplied chemicals. New methods should open up this area of research.

8. the insertion of genes to direct the synthesis of new

proteins and also of high value secondary metabolites. A recent example is the demonstration that genes for antibodies can be expressed in plants.

CONCLUSIONS AND RECOMMENDATIONS

Plant biotechnology offers very good prospects for producing new and better products with less damage to the environment, with greater variety, improved quality and assured supply. This potential has been recognised worldwide and the UK is well placed to take advantage of these developments. Plants with resistances to herbicides, insects and viruses will enter agriculture during the next decade or so providing regulatory authorities allow their dissemination. The environmental advantages from reducing the use of pesticides, fungicides and fertiliser will drive some developments which may otherwise not be commercially viable. The future possibility of engineering crops that can be grown in parts of the third world, such as in the salty plains of Pakistan, could have a major socio-economic impact.

The UK has strengths in the plant sciences, with a number of significant research groups in University departments and AFRC institutes who are well placed to continue the developments in plant biotechnology. Although UK industry moved into plant biotechnology more slowly than some competitors, major UK companies such as ICI, Unilever and Shell now have a growing interest.

Since some of the driving force for developments in plant biotechnology will be for the 'public good', rather than purely commercial, **we recommend that government (AFRC, DoE, DTI, MAFF and SERC), in conjunction with industry and the research community, consider developing a national policy for building on our strengths in plant biotechnology.** This should aim to provide clear guidance on the right balance to take between work of interest to industry

and work to satisfy national requirements.

There has been little exploitation of the potential of plant sources for extraction of chemical feedstocks. The technology to achieve this is largely available but the present commercial case is generally against such exploitation. Nevertheless, we believe that the potential merits further effort; there may be commercial advantage if, for example, oils and fats could be generated through temperate plants. These developments will require research in plant biochemistry and will depend upon the interaction between the agricultural and chemical industries. **We recommend that the Priorities Board for Research and Development in Agriculture and Food consider how they might stimulate the interaction between the agricultural and chemical industries to better exploit the potential use of plants for extraction of chemical feedstocks.**

The development of plant biotechnology in the last ten years has been accompanied by a general decline in the more 'traditional' areas of plant sciences including plant physiology and plant biochemistry. In the medium term, plant biotechnology will make the greatest strides by using past and emerging results from biochemical studies. We have identified gaps in the present UK activities in plant science and **we recommend that a more balanced public sector research effort in the plant sciences is taken; with a co-ordinated programme of molecular, biochemical and physiological studies being established by the AFRC, MRC and SERC.**

Appendix C

BIOTECHNOLOGY IN ANIMAL HEALTH AND HUSBANDRY

INTRODUCTION

Several applications of biotechnology have already provided significant advances in the diagnosis and treatment of animal disease and in improving the quality and utilization of livestock. There is considerable potential for further advance over the next 5-15 years. In this appendix we will consider aspects that do not involve alteration of the genetic make-up of animals (transgenics), which is the subject of appendix C.1

THE PRESENT POSITION, MAJOR RESEARCH OPPORTUNITIES AND POTENTIAL FOR EXPLOITATION

Growth and lactation

Increased efficiency of protein accretion substantially improves animal value. Growth hormone (GH) is known to improve milk production efficiency and carcass composition in farm animals.

In the early 1980s the gene responsible for bovine Growth Hormone (bGH) production was isolated and transferred from animal to bacterial cells to produce large quantities of bovine somatotropin (bST). Injections of 30-50 mg/cow result in significant increases in milk production (10 to 40%) which persist as long as treatment continues. Related programmes with porcine somatotropin (pST) show that body fat can be reduced by up to 80%, feed efficiency improved by 20% and milk production by up to 30% during a sow's lactation period. The use of GH in sheep and chickens is not so advanced, though two months of treatment increases growth rate in lambs by 36% with a 30% reduction in visceral fat.

A number of pharmaceutical companies have invested large sums of money into producing genetically engineered bST. Field trials in Europe have given rise to continued concern since they began in 1987. This is discussed in more detail in appendix A.

Other alternatives are presently being considered for the manipulation of animal performance. These include:

- active immunisation against somatostatin, a hormone that inhibits the release of Growth Hormone (GH)

- raising monoclonal antibodies against GH (which enhance the biological activity of GH by an unknown mechanism)

- immunisation against cell membranes from fat depots

In Vitro Fertilization and Embryo transfer

Exploitation of the genetic potential of male animals has resulted from the ability to cryopreserve sperm and to use small aliquots for artificial insemination of many recipients, in many different locations if required. During the 1960's, techniques for in vitro fertilization and embryo implantation into unrelated recipients were developed in experimental animals at the AFRC Institute in Babraham, Cambridge. Comparable results in sheep, cows and pigs have now been achieved and this technology is being commercialised. The ability to transport frozen embryos across international boundaries is highly valued, both for its economy compared to shipping livestock and for avoiding disease transmission. An important development has been the formation of a new company, Animal Biotechnology Cambridge (ABC) funded largely by venture capital. The recent merger of ABC with a leading animal biotechnology company in Eire, Ovamass Embryos, now places the expanded company in a good international position. Together with Granada in Texas they represent the major commercial contenders in this area, worldwide. Existing technology has rapidly been commercialised and further research and development into new and

advanced techniques offers considerable promise.

In development are techniques for producing embryos of specified sex, useful for example in milk or beef production. Additionally, efficient means of embryo multiplication are being sought so that many (10-100) identical embryos of superior genetic make-up can be produced together.

One technique for embryo multiplication is the mechanical separation of embryo cells at the 4-cell stage and the generation of a complete embryo from each. This may not be economic, and the preferred route is to culture embryonic stem cells (see appendix C.2) and to transplant their nuclei into artificially matured oocytes, which can be obtained in large numbers from abattoir material. The advantage of this approach is the production of very high genetic potential embryos from readily obtained oocytes, and the production of offspring in the most convenient recipient. It is judged that this service could replace much of present practice in animal reproduction and breeding, and the total market could be many tens of £millions.

Sex selection will be achieved by one of the increasingly effective methods for separating non-destructively "X" or "Y" (female- or male-generating) sperm. These include the use of DNA labels or by chromosomal diagnosis of the sex of one of the many identical embryos produced by embryo multiplication.

Diagnostics

Diagnostic products had one of the earliest impacts on animal health (fertility and disease). The first kits launched in the last 5 years have been for pregnancy tests in cows and mares, colibacillosis in calves and pigs, E.coli calf scours and pseudorabies in pigs. By the end of 1986 over 120 test kits suitable for use by the veterinarian or farmer were available, the majority being 'user friendly' with easy to read endpoints.

Fertility monitoring of large animals is currently the largest single area of application for diagnostic kits involving measurement of fertility hormones in blood or milk (progesterone, oestrone sulphate, equine chorionic gonadotrophin). Studies of sperm fertilising ability have identified means by which the fertility of different batches of semen can be predicted. Disease diagnosis by testing in vitro demonstrates the presence of the infective agent in body fluids or tissues, or a response to the pathogen by the infected animal (e.g. specific antibodies, blood components in milk), and is a growing field of investigation. Among companion animals, diagnostic tests are targeted for feline leukaemia, canine heartworm and rheumatoid arthritis; among poultry, large scale screening of avian rheovirus, coccidiosis, salmonellosis and respiratory infections; among large animals, scours in calves and pigs, trichina in pigs, mastitis, leukaemia, infectious bronchitis, brucellosis and transmissible gastroenteritis in cattle.

Major research opportunities relate particularly to technological innovations that increase the speed and improve the sensitivity and simplicity of diagnosis. These include:-

- detection of oestrus with robust and sensitive biosensors for the sex hormones

- rapid and specific disease diagnosis employing monoclonal antibody and polymerase chain reaction techniques for detection of minute traces (protein or nucleic acid) of the pathogen.

Therapeutic drugs and vaccines

Animal therapeutic drugs are proteins derived from advanced technologies that are often analogous to human drugs. With human vaccines even a very low level of serious side-effect is often unacceptable but animal vaccines do not need to meet such stringent

criteria. This allows innovative vaccine approaches to lead the way in animal practice. Balancing this is the constraint that the cost of animal vaccination has to be maintained at a low and economic level.

A monoclonal antibody treatment for calf scours has been developed and passive immunisation will prevent the spread of existing E.coli infection. Other monoclonal antibody treatments are being developed against pseudorabies in piglets, mastitis in cattle and coccidiosis in poultry. Synthetic consensus interferon and various interleukins are being examined for their ability to combat resistance-lowering to viruses and bacteria and formulations believed to contain lymphokines and/or antibodies that trigger an immune response are being tested against cancerous tumours in cattle and horses. Microbially-derived ivermectin has received attention because of its potential to control internal roundworms and lung worms and certain external parasites such as lice and mites. Cloned genes for fertility hormones have been characterised for bovine follicle stimulating hormone and leuteinising hormone with potential use in conjunction with embryo transfer techniques.

Vaccines normally based on killed or attenuated microorganisms may be replaced by use of sub-units of the pathogen. Among the classical vaccines, those for clostridium, Marek's disease, cholera and coccidiosis comprise the largest single agricultural vaccine markets. The first veterinary vaccines using r-DNA technology were Nobi-vac LT, K88 and K99, designed to protect calves and pigs against enteric colibacillosis. The first genetically altered virus vaccine (Omnivac-PRV) was a live virus vaccine for the prevention of Aujesky's disease in pigs. Developments in biotechnology-derived animal vaccines include those against foot-and-mouth virus, wart virus, and mastitis in cattle and various other diseases in cattle, pigs and poultry. It is particularly hoped that new approaches, based on determination of sub-units of relevant epitopes and recombinant proteins, may afford protection from parasitic norms including certain damaging helminths.

Major research opportunities in vaccines relate to the use of subunits, synthetic peptides and recombinant-derived proteins as alternative non-infectious agents. These include:-

- the use of immunogenic vectors to allow 'natural' immunisation with unnatural components

- Cloned immunogen genes are being characterised for many of the major pathogens and this knowledge is important for the design of novel vaccines and the induction of disease resistance

Feed Additives

Animal feed is the single largest input into food production and is the farmer's largest production cost. Biotechnology is expected to have an impact on animal feeds in the longer term through the production of feed additive single-cell proteins, vitamins, enzymes and amino acids.

Recombinant DNA technology may replace conventional microbial and chemical synthesis because of the ability to manipulate microbial organisms and transfer genes into more efficient systems. The biotechnological production of lysine, tryptophan, methionine, cysteine and threonine are presently being investigated. Enzyme additives such as glucose oxidase, beta-glucamase and cellulases are in demand for biomass degradation. Pre-treatment of forage crops and cellulosic biomass with cellulase and xylanase produced by r-DNA techniques is being evaluated for improvement of nutritional quality and digestibility of feed.

This potential use of cellulases and xylanases brings into question the long term suitability of ruminants. These animals with their commensural relationship with rumen microorganisms have provided a pre-existing solution to the indigestibility of plant material but at a cost in feed efficiency. It may be that a shift in the

preferred domestic livestock species is an eventual outcome of these new biotechnologies.

Single cell protein (SCP) from yeast, bacteria or algae is used as an animal feed supplement because of its high protein, essential amino acid, vitamin, mineral and carbohydrate content. Aerobic bacteria using methane and ammonia as feedstocks produce SCP and r-DNA techniques are being used to aid production efficiency of bacteria.

A 10% improvement in forage digestibility could have a value to the UK dairy industry in excess of £10M. Alternative approaches being pursued include:-

- the introduction into rumen bacteria of a synthetic gene, together with techniques for reducing methanosis and proteolysis and increasing nitrogen fixation within the rumen.

- inoculation of silage with genetically-engineered organisms

- tissue specific expression of cellulase genes in transgenic animals

Many farm animals are fed antibiotics for much of their lives and pressure is growing to reduce usage because of the danger of resistant strains building up in the food chain. Biotechnology provides an opportunity to develop new strains of antibiotics to compete with resistant ones. Gene cloning technology has recently been used in Streptomyces for the biosynthesis of useful antibiotics. However, disease control and the introduction of disease resistance into livestock is to be preferred to the prophylactic use of antibiotics, preserving novel antibiotics for human and acute animal treatment.

CONCLUSIONS

The techniques and products of biotechnology have already had a major impact in animal health and husbandry. UK science has initiated several important advances, which have been applied and commercialised in the UK. From a market perspective it is important to note major differences between products aimed at humans and those for animals, margins being much smaller for the latter. Thus highly cost-effective production and distribution is needed, and many applications of biotechnology will probably be too expensive to use in this area.

The Committee note that simply increasing productivity of agricultural animals may not, at this time, be a central objective, at least in the developed world with its present agricultural surpluses. However, **we recommend that the application of biotechnology to improve animal quality, both in terms of consumer preference and of healthier products, for example, leaner or low cholesterol meat, is to be strongly encouraged.**

The Committee welcome the DTI's increasing role in facilitating R&D collaborations and technology transfer in this sector. However, there is some concern at the length of time and the extent of the review and debate needed for relatively small sums of money. This is particularly burdensome for small companies with limited human resources.

The lack of requisite cattle husbandry and research facilities represents a barrier to rapid progress and commercialisation in embryo multiplication in cattle. **We recommend that MAFF, DTI and AFRC consider support for work in embryo multiplication in cattle, in consultation with industry.**

Appendix C.1

ANIMAL TRANSGENESIS

INTRODUCTION

Transgenic animals possess an alteration in their DNA which has been stably incorporated into the genome as a result of intentional experimental intervention. Typically this results from the addition of exogenous foreign DNA or novel DNA constructs. Awareness and interest in this technology (transgenesis) was stimulated by the spectacular success, in 1982, in producing giant mice by injecting a human growth hormone gene fused to a metallothionein promoter into the nucleus of fertilised mouse eggs.

Since early history, man has attempted to improve his livestock and domestic animals by exploiting, through selective breeding, the genetic variation which occurs naturally, both within and between populations. Genetic manipulation gives the scope to accelerate the process of livestock improvement by introducing specific genetic variation into populations under selection. A second opportunity afforded by transgenic technology is the production of medically important proteins in the milk of sheep or cattle. These include insulin, coagulation factors VIII and IX, and alpha-1-antitrypsin. A third approach already realised with 'oncomouse' is the production of transgenic animals with characteristics that provide 'models' of human disease. A fourth area is the use of transgenic animals to study the role of genes in the control of development and physiological processes generally.

TECHNOLOGY

The most common method for introducing alterations in the genetic material is micro-injection directly into the male pronucleus of a fertilised egg; injection into the cytoplasm does not appear to be

effective in higher vertebrates. An area of major present development lies in producing better DNA constructs and incorporating tissue-specific promoters so that the altered characteristics of the cells of the transgenic animals appear in the appropriate place at the appropriate time. It is important to point out that while micro-injection can be reasonably relied on to result in alteration of the genome, the location of the inserted construct is usually random and its level and timing of expression are difficult to control and predict.

Another approach is the use of retrovirus vectors, but again control of location of insertion and level of expression is unpredictable. A further possible disadvantage is the potential risk of mutagenicity associated with retroviral insertion. The production of a strain of selected transgenic animals requires the production of heterozygous offspring which are then inbred to produce, on average, 1 in 4, homozygous transgenics.

Another more recent advance is the use of pluripotent cultured embryonic stem cells (ES cells), transfected with the requisite gene and stimulated to generate a complete embryo. This exciting development will allow much greater control of gene insertion and is considered in more detail in appendix C.2. Another key feature of this method is the potential for gene deletion. Thus far transgenic mice, pigs, sheep, rabbits and cows, and a number of transgenic invertebrates, have been produced. A key goal is to extend this technology to the standard laboratory white rat.

APPLICATIONS OF TRANSGENIC ANIMALS

Transgenic technology is predicted to accelerate breed improvement in agricultural animals in such areas as growth rate, carcass quality (reduced fat, increased muscle), conversion efficiency, milk production, wool production and quality by designer genetic manipulation. Thus far the only substantive results have come from incorporation of the growth hormone gene in pigs - but side effects

due to altered skeletal and joint developments made this untenable. More recently, new GH constructs have circumvented these problems in pigs. For most desired improvements we lack understanding of the genetic elements that regulate the biological characteristics; thus the need is for research into the genetic, biochemical and physiological control mechanisms. It can be anticipated that spin-off from the human genome work will contribute markedly in this area over the next 10-20 years. At present, in most cases it is simply not known what genetic manipulations to make. Another important aspect of husbandry is disease resistance but again, the elements of disease resistance against major animal disease are not well understood and it may be some considerable time before this promise becomes realised. Similar considerations apply to the improvement in environmental resistance for example the ability to tolerate hot dry climates. In each of these areas the use of <u>in vitro</u> fertilisation, embryo multiplication and selection may be the best way forward in the foreseeable future.

Already underway is the development of transgenic animals as 'biochemical factories' particularly, but not exclusively, producing the required product in serum or in secreted form in saliva or milk. Because of the developmental stage at which the transgene is introduced there are no restrictions on interspecies transfer and the recipient animal shows immunological tolerance to the foreign proteins produced. Transgenic sheep, prepared with gene constructs either for human alpha-1-antitrypsin or human Factor IX with DNA sequences from the sheep beta-lactoglobulin promoter, have expressed the gene in the mammary gland with secretion of the gene product into milk. This is seen as an important development, for example, in producing Factor IX for treatment of haemophiliacs and alpha-1-antitrypsin, a serine protease inhibitor increasingly used for the treatment of acute shock syndrome. Traditional blood fractionation is very expensive and cannot supply the potential market. Reliable production of transgenic fowl producing high added value proteins in egg white may be an even more attractive and cost effective system but remains unproven.

Another important area of opportunity is the use of transgenic animals as human genetic, disease, physiological and pharmacological test models. By appropriate design of the transgene a wide variety of changes can be induced without recourse to surgery or drug treatment. Transgenic animals in which specific genes are defective can provide models in which replacement therapy, gene therapy and prevention of sequelae can be evaluated. Severe combined immunodeficiency disease (SCID) is caused by a defective adenosine deaminase and Lesch-Nyhan disease is caused by a defective hypoxanthine guanine phosphoribosyl transferase enzyme. These and many other human syndromes of medical importance might be studied in this way. A very important prospect is being opened-up by developing experimental animal models of disease for pharmaceutical testing and development. This has far reaching implications for human and veterinary medicine and also in areas such as environmental mutagenesis monitoring. A topical example is the opportunity provided by the recent cloning of the human cystic fibrosis gene. It should now be possible to develop transgenic animals with this gene deleted or made dysfunctional, to serve as excellent models for the human condition and thus provide a route to the discovery of novel therapies.

COMMERCIALISATION

A number of new companies have been set up to exploit this technology and several major corporations have incorporated the technology into their research programmes. Interestingly the first commercial transgenic animal, the 'oncomouse', is being sold by Dupont who took the technology from US University researchers. The future for commercialising transgenics will be greatly influenced by the intellectual property position which currently differs in the US and Europe, with novel species or varieties not being patentable in Europe (see section 5.3). There may well be differences of interests between biotechnology companies and traditional breeders and farmers over transgenically improved breeds, and these wider socio-economic factors will need to be

addressed.

THE PRESENT REGULATORY POSITION

The Health and Safety at Work etc (HSW) Act applies to all persons at work in Great Britain. The act also safeguards the health and safety of the public affected by work activities. Regulations have been made under the Act to require notification to HSE of experimental work in genetic manipulation.

In the field of genetic manipulation, the HSE is closely advised by the Advisory Committee on Genetic Manipulation (ACGM). In January 1989 the Committee produced a document entitled 'Guidelines on Work with Transgenic Animals' (ACGM/HSE/NOTE 9). This does not have statutory force but would be taken into account by the HSE Inspectorate and other enforcing authorities when considering whether there is compliance with the statutory requirements.

These new guidelines take into account;

- the safety of the human operator
- the safety of other humans, animals and the environment
- the welfare of the transgenic animal

The introduction of the transgenic animal into the environment is further covered by ACGM/HSE/NOTE 3 ('the planned release of genetically manipulated organisms for agricultural and environmental purposes').

CONCLUSIONS

Transgenics is very much an emerging technology with considerable promise. In the near term the most likely applications are in the production of certain proteins and as an investigatory tool. In the longer term, use for breed improvement will become important.

The Committee applauds ABRC funding of an AFRC Transgenic Animal Programme and the recent establishment of an IRC in Transgenic Animals in Edinburgh, by the Agricultural and Food Research Council with the University. This provides support for an area with major scientific, medical and commercial importance and one in which the UK holds a comparative lead. A further boost would be given to the UK position in this field by funding an effort to establish reliable transgenesis in the laboratory rat. As the basis for so much efficacy and safety testing in the pharmaceutical industry this should be readily commercialisable and then exploited in drug discovery and development. **We recommend that MAFF, AFRC, DTI and possibly MRC should consider how to support research, in collaboration with industry, on reliable transgenesis in the laboratory rat.**

Appendix C.2

STEM CELL BIOLOGY

INTRODUCTION

Animal stem cell biology is an area of scientific strength in the UK. Research in this area of cell and developmental biology is increasingly providing a unifying focus for fundamental research which is aimed at elucidating the coordination and interaction of the complex processes involved in cell diversification in both embryo and adult organisms. Furthermore, increased knowledge of the characteristics of stem cells in the developing embryo and in the adult is underpinning the introduction of new techniques of medical treatment, for example in bone marrow transplants and the possibility for somatic gene therapy of genetic diseases, and will provide new and better methods for the establishment of transgenic animals.

A strategic decision to increase support for stem cell biology could have great benefit by providing improvements in medical therapy and in opening up new commercial possibilities in other areas of biotechnology. It could lead to the establishment of cell engineering and the production of designer cells.

Stem cells are cells which divide both to sustain their own population and to give rise to populations of differentiated cell types. They are therefore essential for the maintenance of many of the tissues of the adult such as blood, skin and lining of the gut.

EMBRYONIC STEM CELLS

In the last twenty years or so, the cellular interactions and development of the early mammalian embryo, in particular the mouse, have been intensively investigated and a cadre of UK research teams

have been world leaders in this area. Such work has recently borne practical fruit in demonstrating the feasibility of preimplantation diagnosis and is likely to have major application in the diagnosis of genetic diseases in human embryos.

In recent years, the isolation of mouse embryonic stem (ES) cells, pluripotential embryonic cells which can be maintained indefinitely in cell culture, yet which can be stimulated to differentiate, has enabled the introduction of powerful techniques for the study of the regulation of gene expression and the role of growth factors in development, and for production of transgenic animals.

ES cells can be introduced into the early embryo and can eventually contribute to all tissues of the adult, including sperm, eggs and their precursors (the germ line). The ability to manipulate and select such cells in culture, prior to introduction into an embryo, enables the introduction of particular genes into experimental mice which, through breeding, subsequently provide a rich source of experimental material. Use of this technique has advantages over the production of transgenic mice by the direct microinjection of gene constructs into fertilised eggs.

The use of embryonic stem cells for transgenic animals (see appendix C.1) has some major advantages since it allows extensive genetic manipulation of the cells in culture, and the selection and screening of the modified cells, prior to whole animal reconstruction. Powerful new techniques are now being developed both for the insertion of DNA into stem cells and for the selection of cells that have been suitably transformed. Work in the genetics department in Cambridge is at the forefront in this area. These techniques can also be applied to other stem cells to engineer designer cells.

Stem cells play a key role in the development of animals. For example the growth of all long bones is due to proliferation of a population of stem cells in the cartilagenous growth plates. There is also increasing evidence that the different cell types in the

development of both the neurons in the brain and the supporting glial population come from stem cell populations.

STEM CELLS IN THE ADULT

In the adult, stem cells play a key role in the renewal and repair of a number of tissues. The most important of these are the stem cells that provide for the production of all the cells in the blood, and the stem cells that generate the cell of both the external and internal lining of the body, the skin and the gut. Stem cells are essential components of tissue transplants such as bone marrow or skin. They provide a major potential vehicle for investigating a number of important diseases and will undoubtedly form the basis for somatic gene therapy in which normal genes may be introduced into the body to replace the function of defective genes. It should also be appreciated that abnormalities in stem cells and their offspring are major causes of carcinomas - by far the most important class of cancers. Further, the major effect of radiation is to damage stem cells in the blood, skin and gut with the consequent severe results such as radiation 'burns' and severe anaemia. Another example of excessive stem cell proliferation is seen in the common skin disease psoriasis.

UK workers, particularly at the Paterson Institute in Manchester, have played a major role in isolating the stem cells of the haemopoietic system. This is a major step forwards and there is now intense effort to identify the factors which control the pathways of differentiation of the stem cells' progeny. Various growth factors seem to be involved in this process of pathway choice and cell proliferation. Manipulation of these stem cells provides the most promising means of introducing new genes into patients with defective genes. Possible diseases that might be treated include thalassaemia, sickle cell anaemia, and immune deficiencies. This technology can also be used to construct designer cells to combat cancer.

CONCLUSION AND RECOMMENDATION

Stem cell biology is an important area where the UK presently holds a lead and we recommend that further efforts are made in promoting this area of science. We support the recent AFRC decision to increase priority for this area and we further recommend that MRC and AFRC consider how they might coordinate an initiative to consolidate on their existing strengths in stem cell biology.

Appendix D

PROTEIN ENGINEERING

INTRODUCTION

Techniques for site-directed mutagenesis were developed in the late 1970's, allowing gene sequences of proteins to be altered virtually at will. This led to the emergence of protein engineering in the early 1980's and represents an area of considerable scientific strength in the UK with many opportunities for exploitation. The UK has led developments in this new technology and recent initiatives have been taken to foster the transfer of these scientific developments into industry.

We can define protein engineering as follows:-

> "protein engineering is the production of a novel or altered protein for a specific purpose. It can be carried out by chemical modification of the protein; but more generally it is achieved by genetic engineering, that is, by the construction or alteration of a gene encoding that protein. The gene is introduced into appropriate host cells, which may be bacterial, plant or animal, such that the product is synthesised there."

Throughout the 1960's and 1970's a considerable amount of research was carried out on natural variants of haemoglobin and mutationally altered proteins. The new techniques of site-directed mutagenesis greatly accelerated this classical molecular genetic approach by directed change. The first genetically altered enzyme to be published was the serine 35 mutation of the tyrosyl tRNA synthetase, in 1982. This was quickly followed by a point mutation in the active site of beta lactamase. Protein engineering expanded

very rapidly after this and is now used as a powerful research technique to evaluate the role of individual amino acids, or of specific segments, in the overall properties of a protein.

UK development of applied protein engineering was stimulated in 1984 when the Biotechnology Directorate of the SERC founded a Protein Engineering Club. Additionally, several MRC developments have been patented and transferred to Celltech. These include those in reshaped human antibodies and in the construction of simple chimaeric antibodies and antibodies with novel effector functions.

The main areas of applied protein engineering to date have been industrial enzymology and medicine. A number of examples of potential useful applications in these areas now follow:-

INDUSTRIAL ENZYMOLOGY

Although no commercial market exists yet for engineered industrial enzymes, it is already certain that protein engineering can be used to improve properties of enzymes in the industrial context. They will often be produced more cheaply than the natural alternative. Based on data from the International Compressed Commodity Trade Statistics Data Base (COMTRADE) of the Statistical Office of the United Nations, the 1985 world export market for industrial enzymes was just over $400M. Denmark accounted for over 30% and West Germany about 14% of the world exports. The UK both exported and imported about 5% of this world trade in enzymes. The current total world market is estimated at £500M per annum, and is said to be growing in volume by 5%/yr, while remaining steady in value. If favourable new processes emerge using engineered enzymes, as seems likely, the market should expand; we might expect new routes to steroid preparations, membrane channels created by proteins, and wide applications in biosensors, for example. It is likely that half the industrial enzyme market will be supplied by engineered enzymes within a decade.

Subtilisin

The world market for subtilisin is about £100M/yr. In addition to domestic washing powders, it is used in a number of industrial cleaning applications.

One commercial target for enzyme engineering has been in making a bleach resistant enzyme. In washing powders, enzyme and bleach are introduced together. The bleach can inactivate the enzyme, both in storage and in the wash. A bleach resistant enzyme was made by replacing an active site methionine, which is otherwise oxidised. However, the overall activity of the mutant enzyme was somewhat impaired and it turns out to be cheaper to encapsulate the bleach in the powder and to use bleach which is activated at high temperatures (when the enzyme has finished its work) than to use a bleach resistant enzyme of slightly lower activity. Thus, bleach resistant enzymes have not found their way into washing powders. However, the enzyme has been marketed in contact lens cleaners where the bleach and enzyme must co-exist in solution for cleaning at room temperature.

The main targets for an engineered subtilisin would now appear to be enhanced thermal stability and an increase in activity toward the acid pH range. The crystal structure of subtilisin was determined in 1969 and its mechanism is well understood. Crystal structures of a number of subtilisin mutants have been analysed by Genentech, including several with artificially introduced sulphur bridges. One such structure has been published, showing a distortion of the protein in forming the bridge, and this particular mutant has reduced thermal stability. It is likely that other sulphur-bridged mutants have been made, with enhanced stability (as has been achieved for other proteins of no particular industrial significance).

Glucose isomerase

The current market for glucose isomerase is estimated at about £150M/yr. It is used in the production of fructose-enriched corn syrup, replacing about 60% of the glucose by its isomer fructose which is approximately three times as sweet. In the US most soft drinks use this material as a sweetener and the production in 1985 was 4M tons (doubled since 1978). In the EC, production of fructose-enriched syrups is limited by quota to 250,000 tons, but there is an expanding market for these products in the Far East.

It is economic to operate the process at a temperature of 65 degrees Centigrade, at which the enzyme has limited lifetime and the cost of enzyme becomes a major expense in production.

The enzyme is obtained from microorganisms such as Streptomyces or Arthrobacter, but may now be available in recombinant forms on an economic basis. Protein engineering of the enzyme to extend its stability in the current process, or to increase the temperature of operation (producing a higher fructose yield) has been sponsored by several groups: Genex in the US, Gist-Brocades and their subsidiary Plant Genetic Systems in France & Belgium, and by the SERC Protein Engineering Club in the UK.

It is known that patents have been lodged for engineered glucose isomerase, but there is as yet no firm report of a mutant enzyme whose properties fully meet the design criteria.

MEDICAL APPLICATIONS

Data on the present or projected size of the enzyme market for pharmaceutical and medical applications is not readily available, but it is clearly large. Data from 'High Technology Business

Research' showed that the 1987 sales of biotechnology therapeutics by US companies totalled $670M. Reasonable predictions for the early 1990's would indicate a world market for medical products from protein engineering to be of the order of $5B. Genentech and Wellcome engaged in an expensive lawsuit to protect their respective interests in tPA. A recent MRC survey recommended regular use of urokinase for a large group at risk from cardiovascular incidents. Monoclonal antibodies are already a significant market. An improved, engineered tPA already exists, and an engineered antibody has been administered clinically with success. Enzymes also have wide application in clinical tests.

Alpha-1-antitrypsin

The engineering of alpha-1-antitrypsin (A1AT) demonstrates the ease with which a protein with enhanced medicinal properties can be developed.

A1AT is the natural inhibitor of leukocytic elastase, a protease which can do serious tissue damage if uncontrolled. Familial tendencies to pulmonary emphysema have been associated with defects in the A1AT gene. A1AT may also be inactivated by oxidation of the methionine residue at the primary inhibition site. It has been shown that in heavy smokers this methionine is oxidised in a high proportion of A1AT molecules.

Workers at Transgene in Strasbourg have engineered variants of A1AT in which this methionine was altered. Since these were expressed in E. coli they lacked the carbohydrate normally associated with the inhibitor, but this had little effect on the inhibition properties. Changing the methionine to leucine produced a protein whose effectiveness against elastase was almost unchanged, but was unaffected by oxidation.

Another plasma protease, antithrombin III, has an important

function in controlling the activity of thrombin in forming blood clots. Antithrombin is a homologue of A1AT, but has arginine at its inhibition site. By changing the methionine at A1AT to arginine an antithrombin was produced which was 50 times more active than antithrombin III. Clinically, heparin is often administered to potentiate the anti-clotting power of the patient's own antithrombin III. The modified A1AT was almost one-third as active as the combination of antithrombin III with heparin.

Although these examples may not in the end be used in clinical situations, they show how a series of single-site mutants can be engineered to have a range of clinically interesting properties.

Tissue plasminogen activator

Tissue plasminogen activator (tPA) is used clinically to disperse blood clots by activating the plasma enzyme plasmin. Recombinant tPA preparations have been produced by several pharmaceutical companies including Genentech, Wellcome and Beecham and Genentech's product, produced in mammalian cell culture has been licensed by the US Food and Drug Administration (FDA).

Engineered variants of tPA have been described which lack two protein domains (81 amino acids), and in which some or all of the glycosylation sites have been removed by converting an asparagine residue at the glycosylation site to glutamine. The recombinant proteins were expressed in mammalian cells. The modified enzymes are less potent than wild-type tPA at very low concentrations (below 10nM), but have almost indistinguishable properties as plasminogen activators at high (clinically relevant) concentrations. They have an advantage over wild-type tPA because they cause less loss of fibrinogen from plasma (probably because they do not activate circulating plasminogen so efficiently, only activating plasminogen bound to fibrin), and because the circulating enzymes have a longer half-life.

Insulin

Improved insulins have been sought for many years, at first by comparing the properties of different vertebrate insulins, and also by chemical modification of the insulin molecule. An engineered insulin for diabetes therapy has been reported by Novo, in collaboration with a group at York University.

The molecule has been modified to inhibit the formation of the normal hexamer, so that it remains monomeric in solution. The engineered insulins are absorbed up to double the speed of human insulin, but with unimpaired biological activity.

Engineered immunoglobulins

It has proved difficult to prepare human monoclonal antibodies with chosen specificity against human tumour cells. Chimaeric antibodies have been made by protein engineering. These contain the active portion of a mouse monoclonal antibody, which binds strongly to the human antigen. The rest of the antibody is human, so as to avoid provoking the damaging response sometimes obtained from a patient when conventional monoclonal mouse or rat antibodies are used. It was originally anticipated, however, that the framework regions of the mouse variable domains would still excite an antibody response in humans. Winter and his colleagues at the MRC Laboratory of Molecular Biology have constructed a 'reshaped' antibody against an antigen which is expressed on virtually all human lymphocytes and monocytes, but absent from stem cells and other blood cells. In the reshaped antibody, only the complementarity-determining regions from the original (rat) antibody are retained; all other sequences are derived from a human antibody. Careful study of known crystal structures of antibodies revealed one point where the human framework region was likely to distort the packing of the complementarity-determining region, and additional mutations were introduced to relieve this

problem. These specially-constructed antibodies were as effective against the antigen (within a factor of two) as the original rat antibody.

Administration of this engineered antibody to several patients has been reported. In two lymphoma patients, lymphoma cells were cleared from the blood, and other symptoms relieved within 20 days. In one patient lymphoma cells reappeared after 100 days and destroyed by further antibody treatment.

It is pleasing to see that an effective agreement for technology transfer of antibody engineering has recently been reached between Cambridge and Wellcome.

Antibodies with novel effector functions have been constructed by Neuberger by fusing enzymes to antigen binding (Fab) regions of antibodies. This gives rise to opportunities in both diagnosis and therapy. For example, antibody-enzyme conjugates may prove invaluable for pro-drug activation in which an antibody directed against a tumour-specific antigen is used to target an enzyme to the tumour. The enzyme can then catalyse the activation of a cytotoxic drug in the vicinity of the tumour.

CATALYTIC ANTIBODIES

Both enzymes and antibodies have the ability to bind specific molecules. In other words, they have the power of molecular recognition. Enzymes differ in that they additionally catalyse chemical group transfers within or between their specifically bound substrate molecules. The catalytic mechanism requires even tighter binding of otherwise unstable reaction pathway intermediates, thereby lowering the activation energy barrier that would otherwise block the chemical reaction pathway from enzyme substrate(s) to product(s). Apart from stabilisation of reaction intermediates

the enzyme also provides, through its own structure at the active site, an environment that enhances a particular chemical transformation. A catalytic antibody is an antibody that has been raised against a stable reaction pathway intermediate. Reactivity of that antibody to the true intermediate stabilises it, and thereby provides a more favourable energetic route from substrate to product.

Recent work in the United States has shown that such antibodies can act as catalysts. The use of transition state mimics in combination with monoclonal hybridoma technology is able to elicit antibodies that show rate accelerations of factors 10^3 to 10^5 over the spontaneous reaction and with particular control of regioselectivity and stereochemistry. The rate accelerations are, to date, below that of enzymes but are comparable in some cases to the use of the enzyme on its unnatural substrate. Reactions catalysed so far have mainly been those of acyl transfer processes (activated ester hydrolysis, bimolecular aminolysis, and lactonization) and of entropically disfavoured processes including a Claisen rearrangement, photodimeration, and alpha-beta elimination.

A recent development is the ability to catalyse the hydrolysis of the amide bond and the hope that such catalysts will operate in vivo to neutralise viruses by peptide cleavage, to deactivate toxins, or possibly to activate zymogens.

The development of catalytic antibodies offers the ability to extend the range of catalysis by proteins to chemical transformations that were not required during the evolution of enzymes.

Recent work using recombinant DNA methods and E Coli expression systems to produce single domain antibodies will be of value in screening for catalytic antibodies.

SUMMARY

Protein engineering is a multidisciplinary technology for the design and construction of proteins. The UK has a strong science base in protein engineering, being at the forefront of many developments. The ability to modify natural proteins to improve catalytic activity, stability and selectivity or for the construction of chimeric molecules that combine the properties of differing natural proteins offers new possibilities for industrial, clinical or agricultural applications. Recent initiatives such as the setting up of an IRC (in Cambridge) and the announcement of a LINK programme in protein engineering will continue to provide the impetus for developments in this topic.

There is a concern, however, at the ability of UK industry to gain by the efficient transfer of this expertise. This will depend, in part, on the level of skill in the supporting sciences such as three dimensional structure determination, molecular modelling, 2-D NMR and crystallography. There is, at present, insufficient support for these areas. Biotechnology has pulled a lot of science into the commercial arena, but at the expense of the basic science upon which it is founded and we see this as a major market impediment for the exploitation of the protein engineering expertise in the UK. **We recommend that DES, via the Research Councils, and DTI carefully consider the balance of funding in protein engineering, giving equal priority to the supporting sciences that will be needed for the industry to fully exploit the developments.**

Appendix E

The members of the Emerging Technologies Committee are:

*Professor L Maunder (Chairman)	Professor of Mechanical Engineering, University of Newcastle
Professor M Ashby, FRS, FEng	Professor of Engineering, Cambridge
Mr T Broughton	Director of Design Engineering, Rolls-Royce plc, Derby
Professor J Crookall	Head of College, Cranfield Institute of Technology
Professor D E N Davies CBE, FEng, FRS	Vice-Chancellor, University of Technology, Loughborough
Professor G Edge	Chief Executive, Scientific Generics, Cambridge
Dr P Garland	Chief Executive, The Institute of Cancer Research : The Royal Cancer Hospital
Professor A Kelly CBE, FEng, FRS	Vice-Chancellor, University of Surrey
*Professor D K Peters FRCP	Regius Professor of Physic, Cambridge University Clinical School
Dr T Rink	Vice President, Research, Smith Kline and French Research Ltd
*Professor J M Robertson	Department of Electrical Engineering, University of Edinburgh
Professor B Shackel	Department of Human Sciences, (HUSAT), University of Technology, Loughborough
*Dr D Smith	Consultant
Dr W Maton-Howarth (Secretary)	ACOST Secretariat, Cabinet Office
Mr B Arthur	Assessor, DTI
Dr R Whelan	Assessor, CEST

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* ACOST Members

The members of the Life Sciences sub-group of the Emerging Technolgies Committee are;

*Professor D K Peters FRCP (Chairman)	Regius Professor of Physic, Cambridge University Clinical School
Dr P Garland	Chief Executive, The Institute of Cancer Research : The Royal Cancer Hospital
Dr T Rink	Vice President, Research, Smith Kline and French Research Ltd
Professor L Wolpert, FRS	Department of Anatomy and Developmental Biology, University College and Middlesex School of Medicine, London
Dr W Maton-Howarth (Secretary)	ACOST Secretariat, Cabinet Office
Dr I Lawrence (Assessor)	RTP, DTI

Appendix F

The Committee would like to thank the following for their assistance during the course of this investigation;-

Overview papers

1.	Dr P Warren	The Royal Society (on behalf of the Spinks Club)

A paper reviewing developments in selected areas of biotechnology since the publication of the Spinks Report.

2.	Dr R Dietz & Dr W G Potter	DTI SERC

A joint paper reviewing the main industrial sectors concerned with biotechnology.

3.	Dr D Secher	Celltech

A paper on the opportunities for biotechnology in pharmaceuticals and diagnostics

Non-Technical Factors : Appendix A

Written views were provided by the following;-

- Professor J E Beringer	Chairman of Intentional Introductions sub-Committee of ACGM.
- Professor F J Bourne	Director AFRC Institute for Animal Health
- Professor D C Burke	Vice Chancellor UEA and Chairman ACNFP
- Dr E C Dart	Research Director, ICI Seeds
- Mrs A Foster	Food Policy Adviser, National Consumer Council
- Sir Hans Kornberg	Chairman, ACGM
- Dr D J Jeffries	Head of Division of Virology, St Mary's Hospital and member of ACGM
- Professor A J F Webster	Department of Animal Husbandry, Bristol University
- Dr E Yoxen	Project leader, CEST and joint author of the report by the European Foundation for the Improvement of Living and Working conditions entitled 'The Social Impact of Biotechnology'.
- HSE	Short paper and 'guidelines on work with transgenic animals' (ACGM/HSE/NOTE 9)

A detailed commentary on an early draft of appendix A was provided by Sir Hans Kornberg, Chairman, ACGM

Plant Biotechnology : Appendix B

1. Professor R B Flavell — Director of the John Innes Institute of the AFRC Institute of Plant Science Research

for a position paper on plant biotechnology.

2. Professor D Grierson — Department of Physiology and Environmental Science, University of Nottingham School of Agriculture

for a commentary on Professor Flavell's paper.

3. Dr E C Dart — Research Director, ICI Seeds, Jealott's Hill Research Station, Bracknell.

for a commentary on Professor Flavell's paper.

4. Dr R A Leigh — AFRC Institute of Arable Crops Research, Rothamsted Experimental Station, Harpenden

for a short additional paper on plant biotechnology

Animal Biotechnology : Appendix C

1. Dr B Heap — Head of AFRC Institute of Animal physiology and Genetics Research, Cambridge Research Station.

for a position paper on animal biotechnology.

2. Dr M Evans — Department of Genetics, Cambridge University.

for a commentary on Dr Heap's paper and for an additional paper on animal transgenesis.

3. Dr D A Rees & Dr M Probert — MRC

for a paper on the MRC activities in Stem Cell Biology

Protein Engineering : Appendix D

1. Professor D M Blow — Department of Physics, Imperial College of Science, Technology and Medicine, London University

for a position paper on protein engineering.

2. Dr G Winter — MRC Laboratory of Molecular Biology, Cambridge

for a commentary on Professor Blow's paper

Additional Information on Celltech

1. Mr G Fairtlough — Celltech

SCI+TECH : Budget PT10

CF R B/F when PERB's minute arrives AT 9/2

ANDREW TURNBULL

9 February 1990

BRITISH STAFF IN THE EUROPEAN INSTITUTIONS

Following this subject's being raised in the Prime Minister's meeting last week with Sir Francis Tombs, I understand that Sir Robin Butler will probably be minuting the Prime Minister about it next week.

He will I imagine set out various ideas which are emerging from a review of the subject which has already been underway for a few months in the European Secretariat under energetic direction from John Mogg. He will also no doubt underline how bad the situation is, and how it is getting worse through a dearth of British candidates (let alone successful candidates) for the Commission's graduate recruitment grades.

Any lasting solution in my view is going to need a good dose of new thinking and the full weight of the Prime Minister behind it in order to get Departments to take it more seriously.

I have been keeping in touch with John Mogg on the Cabinet Office review and would appreciate the opportunity to comment on Sir Robin Butler's minute.

John Mills

JOHN MILLS

10 DOWNING STREET

LONDON SW1A 2AA

From the Private Secretary

6 February 1990

ACOST REPORT: DEVELOPMENTS IN BIOTECHNOLOGY

I attach a copy of the letter which Sir Francis Tombs sent to the Prime Minister with the ACOST Report on Developments in Biotechnology. She has given Sir Francis permission to publish the Report and has asked the Chief Scientific Adviser to co-ordinate the Government response. The Cabinet Office will shortly be forwarding copies of the Report and calling for Departments' contributions to the response which it is planned to publish separately.

I am copying this letter to the Private Secretaries to the members of E(ST) and to Sir Robin Butler.

PAUL GRAY

Simon Webb, Esq.,
Ministry of Defence.

W0366

MR TURNBULL - No. 10 6 February 1990

ACOST REPORT ON DEVELOPMENTS IN BIOTECHNOLOGY

Your minute of 1 February crossed with mine of 30 January to Paul Gray in which I advised on how to deal with the ACOST report on Developments in Biotechnology. I understand that Paul now has matters in hand.

2. The Government response will be sent by the Prime Minister to Sir Francis Tombs under a short covering letter. The form in which it will be subsequently published will be decided when we are further down the road. There is no standardised procedure on this.

JOHN FAIRCLOUGH
Chief Scientific Adviser

SCIENCE: Budget Pt 10

file LPO

(C: \ Tombs)

cc C.O.

10 DOWNING STREET

LONDON SW1A 2AA

THE PRIME MINISTER

6 February 1990

Dear Sir Francis.

ACOST REPORT: DEVELOPMENTS IN BIOTECHNOLOGY

Thank you for your letter of 31 January and for the ACOST Report on Developments in Biotechnology. There have been major developments since the Spinks Report in 1980 and I am grateful for the Committee's new recommendations on how we should tackle the obstacles to progress in this very important area.

I am arranging for a formal Government response to your Report and am happy to see the Report published in the meantime. The Cabinet Office will advise you shortly on any factual changes to your text which may be necessary.

Yours sincerely

Margaret Thatcher

Sir Francis Tombs.

CC 90

ELIZABETH HOUSE
YORK ROAD
LONDON SE1 7PH
01-934 9000

Paul Gray Esq
10 Downing Street
LONDON SW1A 2AA

- 5 FEB 1990

Dear Paul

with PG?

RESEARCH COUNCILS - THE AFRC AND THE NERC

Having received clearance from you as sought in my letter of 29 January, my Secretary of State wrote to Sir David Phillips as proposed.

I am copying his letter to you and to the Private Secretaries to Ministers in membership of E(ST), to Sir Robin Butler and the Chief Scientific Adviser.

Yours

Stephen

S T CROWNE
Private Secretary

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File
a:\pps\ACOST
(mem)

10 DOWNING STREET

LONDON SW1A 2AA

From the Principal Private Secretary

SIR JOHN FAIRCLOUGH
CABINET OFFICE

ACOST

In my record of the Prime Minister's meeting with Sir Francis Tombs on 31 January, I overlooked the brief discussion on the size of ACOST. Sir Francis argued that a committee of 20 was desirable. For much of its work ACOST broke down into smaller groups. There were four standing groups and four special study groups. To ensure that these were properly staffed without imposing an excessive burden on people who had many other demands on their time, it was desirable to have a pool of around 20. After a brief discussion, the Prime Minister agreed that ACOST should continue to have 20 members. She commented that the more important thing was to ensure that the meetings were effective.

I am copying this minute to Sir Robin Butler, Cabinet Office.

ANDREW TURNBULL
5 FEBRUARY 1990

KK

PRIME MINISTER

ACOST REPORT: DEVELOPMENTS IN BIOTECHNOLOGY

You may wish to glance at this ACOST Report which has just been submitted by Sir Francis Tombs. A one-page summary prepared by the Cabinet Office is immediately above the Report itself.

The handling proposed is that you should reply to Sir Francis Tombs agreeing that the Report should be published, to be followed in due course by a Government response which the Cabinet Office will co-ordinate.

Content to sign the attached letter?

PAUL GRAY
5 February 1990

file
(C:\ppsl\ACOST.das)

10 DOWNING STREET

LONDON SW1A 2AA

From the Principal Private Secretary

SIR JOHN FAIRCLOUGH
CABINET OFFICE

ACOST REPORT ON DEVELOPMENTS IN BIOTECHNOLOGY

Sir Francis Tombs has now written to the Prime Minister submitting this report. He has sought agreement for it to be published in advance of the Government response. I would be grateful for early advice on whether there are any objections to this and on whether there are any factual changes which we would want to seek before it is published.

BF.

Could the Cabinet Office also take on the task of co-ordinating the Government's response? Please could you also advise on the form this should take.

ANDREW TURNBULL
1 February 1990

CONFIDENTIAL

10 DOWNING STREET

LONDON SW1A 2AA

From the Private Secretary

31 January 1990

Dear Stephen,

RESEARCH COUNCILS - THE AFRC AND NERC

Thank you for your letter of 29 January which the Prime Minister has seen. She is content with the proposed terms of your Secretary of State's letter to Sir David Phillips.

I am copying this letter to the Private Secretaries to the members of E(ST) and to Sir Robin Butler and the Chief Scientific Adviser.

Yours,
Paul

Paul Gray

S.T. Crowne, Esq.,
Department of Education and Science.

CONFIDENTIAL

ACOST
Advisory Council on Science and Technology
70 Whitehall, London SW1A 2AS
01-270- 0109

1-2

The Rt Hon Margaret Thatcher MP
The Prime Minister
10 Downing Street
London SW1

31 January 1990

in attached folder.

Dear Prime Minister,

DEVELOPMENTS IN BIOTECHNOLOGY

You may recall that the report of a joint ACARD, ABRC and Royal Society Working Party on Biotechnology, chaired by Dr A Spinks, was published in March 1980. Developments in this important field have continued at a rapid pace and we considered it timely to re-examine the subject.

I am enclosing a report approved by the Council on recent developments in biotechnology which has been prepared by our Emerging Technologies Committee chaired by Professor Maunder. Applications of the biological sciences will have a major impact in future years and present developments will lead to many benefits for society. These include the provision of better health care, improvements to the environment, to food production and food quality and consumer choice. There are however difficult hurdles to overcome, one of the most important of which is the adverse public perception to aspects of genetic manipulation.

The report makes a number of recommendations which we would like the Government to consider. They are directed at appropriate Government departments. Some apply to industry and to the Research Councils. Others reflect the broad nature of the subject and recommend actions that are applicable across Government.

Secretariat:
Telephone 01-270 0105
Telex 27582 CABOFF G
Fax 01-270 0462
Prestel 21 999 3466
Gold 81 MPO 005

I should be very grateful for your permission to publish the report. We would prefer to do this before a formal Government response is prepared but we would of course take account of any factual changes which the Government advises us as being necessary.

Yours sincerely,

Francis Tombs

SIR FRANCIS TOMBS

SUMMARY OF THE RECOMMENDATIONS IN ACOST'S REPORT ON DEVELOPMENTS IN BIOTECHNOLOGY

The emphasis in ACOST's recommendations is on coordination of developments to ensure that the UK effort in biotechnology comes together in a coherent and sustainable programme - with proper attention being given to supporting disciplines and education of both those directly involved and the general public.

In particular ACOST recommend that:

i) coordination between Research Councils should be improved,

ii) DES, DTI, Research Councils and industry should look together at future manpower needs.

2. ACOST wish to see UK strengths developed:

- in plant biotechnology - by providing guidance and encouragement to universities and the research institutes in areas of high commercial potential (eg antibiotics from plants) and by stimulating interaction between the agricultural and chemical industries.

- in embryonal stem cell biology - by a strategic Government decision to support this field and by maintaining the high priority of the work on automatic sequencing and mapping the human genome

- in animal biotechnology - by considering programmes for embryo multiplication in cattle and for increasing the efficiency of methods for constructing transgenic laboratory animals.

3. Exploitation by industry of the initiatives in protein engineering will place demands on related skills in chemistry such as molecular modelling, crystallography etc - and ACOST consider that these should receive increased support.

4. ACOST recommend that Research institutes try for greater added value from collaboration with European partners.

5. ACOST would like to see Government Departments doing more to promote public understanding and support for biotechnology - for instance by increasing public involvement in Government Committees. They would like to see the Interdepartmental Committee on Biotechnology (ICBT) taking the lead in providing for the public a balanced programme of information on major aspects of biotechnology.

6. ACOST recommend that a detailed and systematic analysis of ethical issues such as genetic manipulation should be considered, possibly using ad hoc Committees similar to the Warnock Committee.

Cabinet Office
29/1/90

SUBJECT or MASTER.

FILE.

SH

MEETING RECORD

10 DOWNING STREET

LONDON SW1A 2AA

From the Principal Private Secretary

SIR JOHN FAIRCLOUGH

CABINET OFFICE

MEETING WITH SIR FRANCIS TOMBS: ACOST 14 MARCH

Sir Francis Tombs came to see the Prime Minister today to discuss the ACOST work programme on the agenda for the 14 March meeting which the Prime Minister will be attending.

Agenda

It was agreed that there should be three presentations on:

- the development of the Science Base since 1979;
- adaptive biology;
- advanced manufacturing technology;

Sir Francis said the study of the Science Base looked back over the past ten years and would serve to disabuse a number of current notions. It showed that funding from the Research Councils had increased significantly in real terms (though funding from the UGC/UFC had remained roughly constant); that fears about under-funded Alphas were overdone; and that the majority of researchers were satisfied with the equipment available to them. Sir Francis was worried about the lack of accountability of funding through the UFC. Much of this was intended to finance the overheads of the "well-found laboratory". In future, resources required to meet overheads would be built into the specific research grants from the Research Councils. He felt this was a better system. The Prime Minister was concerned that younger researchers found it difficult to obtain small grants and she suggested the establishment of a trust.
Sir Francis agreed that there might be a funding gap between the £10,000 maximum for Royal Society grants and the £30,000 minimum for the Research Council grants. He agreed to think further about this problem. You suggested that universities might be given specific responsibilities in this area.

Future Work Programmes

Sir Francis set out the areas to which ACOST would be giving priority:

KK

(i) transport, where he felt that insufficient research had been done on the relative contribution of different modes on energy consumption and CO2 production;

(ii) the non-nuclear scientific work being undertaken by the UKAEA. ACOST had been sceptical of the case for retaining scientific resources in UKAEA and bringing in new lines of business to replace a run-down in nuclear research rather than dispersing the scientific resources to new uses. Part of the UKAEA work was into fuel cells. Sir Francis felt that the best pay off came not from new energy sources but from increasing the conversion efficiency and the utilisation efficiency of existing fuels;

(iii) ACOST had now established a Standing Committee on the environment which would look not only at ways in which changes to the climate could be avoided but also at ways of adapting should the change take place - hence the interest in adaptive biology.

Quality of Scientific Advice in Departments

Sir Francis felt there had been a decline in the quality of scientific advice. This was apparently because scientists were being appointed at less senior levels and apparently because those appointed had too little experience outside Government, eg. in industry or academia. It was agreed that you would look into the issues and make suggestions on the ways in which the quality of advice could be sustained.

British Scientific Activity in the Community

Sir Francis felt that Britain received too small a proportion of Community scientific programmes. In part this was because Britain was seriously under-represented in the scientific directorates. He also felt that departments should be more ready to take the initiative in programming UK views at the earlier planning stages of scientific programmes. The Prime Minister felt that this was a manifestation of a wider programme. While Britain had its fair share of the most senior posts in the Commission, it was under-represented at the middle and lower levels and this was as true for the scientific directorates as elsewhere. She would ask Sir Robin Butler to consider what could be done to overcome this. While agreeing that it was important for the UK views to be heard at the planning stage of scientific programmes it was important that departments should not act in such a way as to stimulate more spending by the Community.

I am copying this minute to Sir Robin Butler.

AT

ANDREW TURNBULL

31 January 1990

W0357

MR PAUL GRAY

30 January 1990

ACOST REPORT: DEVELOPMENTS IN BIOTECHNOLOGY

Sir Francis Tombs will shortly be sending the Prime Minister a copy of ACOST's Report on Developments in Biotechnology. A one-page summary of the main points in the Report is attached.

2. I am also attaching a draft letter, for the Prime Minister to send to Sir Francis acknowledging the Report, and a draft minute for you to send to Departments.

3. I am copying this minute to Richard Wilson and Sonia Phippard.

JOHN FAIRCLOUGH
Chief Scientific Adviser

SUMMARY OF THE RECOMMENDATIONS IN ACOST'S REPORT ON DEVELOPMENTS IN BIOTECHNOLOGY

The emphasis in ACOST's recommendations is on coordination of developments to ensure that the UK effort in biotechnology comes together in a coherent and sustainable programme - with proper attention being given to supporting disciplines and education of both those directly involved and the general public.

In particular ACOST recommend that:

i) coordination between Research Councils should be improved,

ii) DES, DTI, Research Councils and industry should look together at future manpower needs.

2. ACOST wish to see UK strengths developed:

- in plant biotechnology - by providing guidance and encouragement to universities and the research institutes in areas of high commercial potential (eg antibiotics from plants) and by stimulating interaction between the agricultural and chemical industries.

- in embryonal stem cell biology - by a strategic Government decision to support this field and by maintaining the high priority of the work on automatic sequencing and mapping the human genome

- in animal biotechnology - by considering programmes for embryo multiplication in cattle and for increasing the efficiency of methods for constructing transgenic laboratory animals.

3. Exploitation by industry of the initiatives in protein engineering will place demands on related skills in chemistry such as molecular modelling, crystallography etc - and ACOST consider that these should receive increased support.

4. ACOST recommend that Research institutes try for greater added value from collaboration with European partners.

5. ACOST would like to see Government Departments doing more to promote public understanding and support for biotechnology - for instance by increasing public involvement in Government Committees. They would like to see the Interdepartmental Committee on Biotechnology (ICBT) taking the lead in providing for the public a balanced programme of information on major aspects of biotechnology.

6. ACOST recommend that a detailed and systematic analysis of ethical issues such as genetic manipulation should be considered, possibly using ad hoc Committees similar to the Warnock Committee.

Cabinet Office
29/1/90

C:\ Tombs KCB

DRAFT LETTER FROM THE PRIME MINISTER TO SIR FRANCIS TOMBS

ACOST REPORT: DEVELOPMENTS IN BIOTECHNOLOGY

Thank you for your letter of ~~2~~ 31 January and for the ACOST Report on Developments in Biotechnology. There have been major developments since the Spinks Report in 1980 and I am grateful for the Committee's new recommendations on how we should tackle the obstacles to progress in this very important area.

I am arranging for a formal Government response to your Report and am happy to see the Report published in the meantime. The Cabinet Office will advise you shortly on any factual changes to your text which may be necessary.

c/ Webb

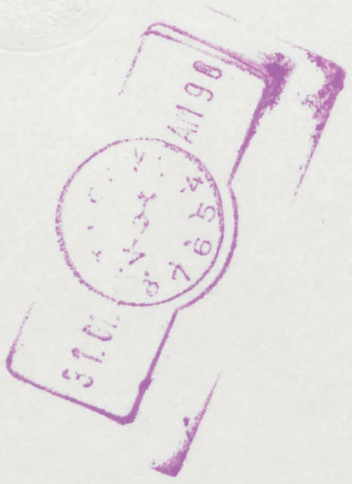
DRAFT LETTER FROM PAUL GRAY TO THE PRIVATE SECRETARIES OF E(ST) MINISTERS

ACOST REPORT: DEVELOPMENTS IN BIOTECHNOLOGY

Attached is a copy of the letter which Sir Francis Tombs sent to the Prime Minister with the ACOST Report on Developments in Biotechnology. She has given Sir Francis permission to publish the Report and has asked the Chief Scientific Adviser to coordinate the Government response. The Cabinet Office will shortly be forwarding copies of the Report and calling for Department's contributions to the response which it is planned to publish separately.

Com b E(ST) HRthe.

SCIENCE : Budget Pt 10 ....



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PRIME MINISTER

RESEARCH COUNCILS

You saw last night, but did not comment on, John MacGregor's proposed draft letter to David Phillips about the ABRC proposal on Research Council reorganisation (attached).

George Guise has suggested some possible alternative drafting as marked, but I feel this may go rather beyond the spirit of the E(ST) conclusions.

(i) Content with the John MacGregor draft? Yes

OR

(ii) Prefer any amendments?

PMG

(PAUL GRAY)
30 January 1990
a:\economic\research (srw)

SECRETARY OF STATE FOR EDUCATION AND SCIENCE

ELIZABETH HOUSE
YORK ROAD
LONDON SE1 7PH
01-934 9000

CEPS

Prime Minister
Content with the attached response following last week's E(ST) discussion?
ARC 6
29/1

29 JAN 1990

CONFIDENTIAL

Paul Gray Esq
10 Downing Street
LONDON SW1A 2AA

Dear Paul

RESEARCH COUNCILS - THE AFRC AND THE NERC

At last Thursday's meeting of ~~E(ST)~~ attached, it was agreed that my Secretary of State should circulate a draft of his proposed response to the ABRC.

This is attached and I should be most grateful to receive the Prime Minister's clearance for it to issue. If at all possible, it would be helpful to have this by first thing on Wednesday morning so that the letter can be handed over to Sir David Phillips before Mr MacGregor appears at the ABRC's meeting at 10.30 am.

I am copying this letter to the Private Secretaries to Ministers in membership of E(ST) and to Sir Robin Butler and the Chief Scientific Adviser.

Yours

Stephen

S T CROWNE
Private Secretary

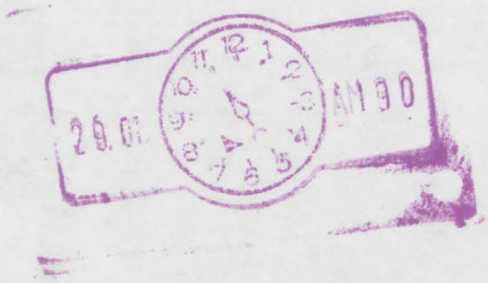
DRAFT LETTER FROM SECRETARY OF STATE FOR EDUCATION AND SCIENCE TO SEND TO SIR DAVID PHILLIPS, CHAIRMAN OF THE ABRC

Thank you for your letter of 1 December, which supplemented the advice in your letter of 15 November about the structure of the Research Council System.

Your further letter asked for guidance on the suggestion that a small working group should be established under ABRC auspices to examine the practicalities of achieving a closer association of the AFRC and NERC, possibly leading to a merger of the AFRC and NERC as recommended by the House of Lords Select Committee. The purpose would be to achieve closer coordination of the research programmes of these Councils, in particular in terrestrial life sciences.

We have considered this proposal in the light of the decision that the ABRC should be reconstituted from 1 April, and have concluded that we would prefer to let the 'new' ABRC take forward the question of improving cooperation between all the Councils, within the existing Research Council structure. The need for greater cooperation was a major factor in our decision to reconstitute the Board and give it a new remit, and we would now expect the 'new' Board to give urgent attention to carrying this into effect.

As with our earlier exchange, I shall be placing copies of our letters before Parliament.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ANDREW TURNBULL 29 January 1990

MEETING WITH SIR FRANCIS TOMBS

I have the following comments on Fairclough's brief:

1. Agenda for March ACOST meeting

The ACOST meeting should run for 2 hours maximum. It will then be possible to allocate 30 minutes for three specific subjects based on 15 minutes of presentation followed by 15 minutes of discussion. There will then be time for preamble and for some general discussion towards the end.

The core of the meeting should consist of specific examples of scientific advance in the three chosen areas. Tombs should be headed off presentations about funding mechanisms and administrative structures. These are important subjects for his private meeting with the PM but not suitable for open debate with ACOST.

Of the specific subjects offered, **adaptive biology** sounds the most fascinating and should give us all a chance to learn something new. Practically all the work on climate change is about how to measure it or how to stop it. This subject is about how to react to it and even to turn it to advantage!

International cooperation is topical and important. Specific examples and results should be addressed rather than organisation and money. The early Framework papers for E(ST) were filled with spending projections. Only after UK insistence did we get some indication of the specific proposals in scientific language.

Covering CONFIDENTIAL

The biggest international collaboration is CERN where much has been happening since LEP* was commissioned in the summer. Since Professor Chris Llewelyn-Smith, the Chairman of the CERN policy committee and recently appointed to ACOST, should be at the meeting, it would be appropriate to invite him to comment. I know him well and he is very sound on financial matters as well as scientific ones. It was his thinking that led to the recalculation of Britain's sterling contribution to CERN. This will save us some £10 million annually.

Advanced manufacturing technology seems oddly placed unless we are to hear evidence of how British industry is increasing its investment. The Prime Minister has seen an excellent example of what can be achieved at Warwick University where academic brain power is harnessed by the energy of Kumar Bhattacharyya and funded by industry. It is worth noting that in 1989/90 the DTI will still spend over £500 million of taxpayers' money on science and technology although this is due to fall to below £400 million by 1991/92.

2. **Dual Funding**

The question of dual funding is pertinent to the private meeting with Tombs. Last week at E(ST) the research councils were found wanting in many respects but as least they account for every penny spent even if too much goes on bureaucracy. By contrast, the UFC, spending some £800 million annually, does not track the expenditure to its final destination at the research bench. I am told that a 'good working assumption' is that 60% goes on teaching and 40% on research! The problem is that the universities do not have proper cost accounts. It would therefore be appropriate to discuss dual funding but not at an open meeting of ACOST.

* Large electron-positron collider

It might be possible to address this matter within the overall remit David Phillips is receiving for the new ABRC as discussed last week. Again, the matter could be a subject for ACOST providing it were given a specific remit for advice to government. It is a tricky problem, with potential for ruffling many academic feathers! Nevertheless it is a most important issue and Tombs is right to raise it.

3. The Size of ACOST

ACOST members are unpaid and the only direct cost is a four person secretariat in the Cabinet Office. The main argument for cutting it down is to make it work more efficiently. However, most of the specific ACOST work is done by sub-groups drawn from the membership and sometimes including co-opted persons from outside. There is now a stronger representation from basic science than had ACARD. The Acost membership is set out in Annex 1.

The quality of membership, from whom working groups may be drawn, is more important than absolute size. It is therefore less necessary than with research councils and other Whitehall bureaucracies, to limit size on cost grounds. It may however be that membership would be more prestigious and therefore attract even better people if the total size were cut from 20 to say 16. This is an argument which should be explored with Tombs.

3. Future work of ACOST

It would be good to examine Tombs on the specific objectives of the new environmental sub-committee. We have so many scientific programmes on environment already. In particular, the work of the IPCC conducted by John Houghton at the Met

Office is most impressive as is the WOCE. The terms of reference of this new ACOST standing committee are set out in Annex 2 where you will see much talk of the relationship between economic and social progress with the environment!

The Prime Minister should emphasise that scientific work should be about the physics and chemistry taking place in the environment not economic and social projections which are themselves based on uncertain physical science!

Here are some thoughts for further ACOST work:

(i) Where do we stand on **transport research**? Is HMG over or under funding? The DTP currently spends £28 million per annum on transport research of which only £10 million is associated with its statutory duties. Should all this balance be funded by industry or does government have some responsibility for transport research beyond statutory requirements?

(ii) **Health research**, where there has been a new appointment of a Chief of R&D. ACOST could also look at the opportunities for small high tech companies performing contract work for the NHS.

(iii) The basic science conducted by the UKAEA. What is the consequence to applied **nuclear research** of keeping the business in the government sector?

(iv) The effect of **privatisation** on research in those industries concerned.

4. Departmental Chief Scientists

Tombs is concerned about the apparent decline of Chief Scientists

posts. My view is contrary. I believe the dismantling of senior scientific posts is quite consistent with government policy of moving applied research into the private sector.

When a department handles scientific detail in order to fulfil its procurement role, it must employ highly qualified people who can either give the advice themselves or find the best place to get it. This is true of departments like Defence, Environment or Health. It is less self-evident that departments like the DTI or the DES should have much in-house scientific capability.

RECOMMENDATIONS

1. Have the March meeting concentrate on scientific achievements rather than philosophies of how money is spent.

2. The size of ACOST is less important than the quality of its membership.

3. The PM should probe Tombs on the work of the new environmental standing committee.

4. The PM should not be too concerned about the disappearance of Chief Scientists!

GEORGE GUISE

NB

I was initially concerned to read that the Research Councils are 'staffing an office in Brussels'! In fact this is a

two person outfit designed to ensure that when Euro money is spent Britain gets its fair share. It has not been set up as a lobbying activity for more spending. It would be no bad thing for the PM to reinforce this although it is more a matter for David Phillips than Francis Tombs.

Annex 1 Membership of ACOST

Annex 2 Terms of Reference of New Environmental Committee.

ANNEX 1

The Full list of ACOST members is as follows -

Sir Francis Tombs FEng (Chairman)	Chairman, Rolls-Royce plc
Prof Roy Anderson FRS	Dept of Pure & Applied Biology, Imperial College of Science
Prof Thomas Blundell FRS	Dept Crystallography, Birkbeck College
Lord Chilver FRS FEng CBIM	Chairman, University Funding Council
Dr Peter Doyle	Director of Research and Technology Imperial Chemical Industries plc
Mr Anthony Gill BSc FEng	Chairman, Lucas Industries plc
Mr Terry Harrison FEng,BSc,FIMechE,FIMarE	Chairman, Northern Engineering Industries plc
Mr Ian Harvey	Chief Executive, British Technology Group
Sir Graham Hills FRSC FRSE	Principal & Vice Chancellor, University of Strathclyde
Prof Leonard Maunder OBE FEng	Dept of Mechanical Engineering, University of Newcastle-upon-Tyne
Mr David McMurtry	Chairman, Renishaw plc
Prof Sir David Phillips FRS	Chairman of the Advisory Board for the Research Councils
Prof Keith Peters FRCP	Regius Professor of Physic, Cambridge University Clinical School
Sir George Porter PRS	President of the Royal Society
Prof Gareth Roberts FRS	Director of Research, Thorn EMI and Professor of Engineering Science, University of Oxford
Prof John Robertson	Dept Electrical Engineering, University of Edinburgh
Dr Alan Rudge OBE FEng FRSA	Director of Research and Technology British Telecom plc
Sir Alfred Shepperd	Chairman, The Wellcome Foundation Ltd
Prof Christopher Llewellyn Smith FRS	Chairman of Physics, University of Oxford
Dr David Smith	Consultant

ANNEX 2

ACOST STANDING COMMITTEE ON THE ENVIRONMENT
TERMS OF REFERENCE

1. The environment, globally, regionally and locally will be one of the major national concerns in the next decade. ACOST has reported on some of the issues and set up a Working Group to advise the Government in 1988 on ozone layer depletion and greenhouse gases. Subsequently a report was published by NERC at the request of ACOST called 'Our Future World'.

2. The Government requires advice on the level of research in environment matters and appropriate mechanisms which is independent. This will cover global issues including scientific matters like chemical and biological changes; also regional issues such as acid rain, and local ones such as surface water quality, waste disposal, air and noise pollution, soil science.

3. An important aspect is the influence of environment on future economic and social progress in the UK. A balance has to be struck between socially desirable needs and cost. More involvement in international activities may be needed.

4. Government policies for energy and transport will in the future be increasingly concerned with environmental issues and will need reviewing from this point of view.

5. In the light of these factors ACOST will undertake a more extensive activity and an Environment Standing Committee will be set up with the following terms of reference.

i. To investigate the research needs to solve environment problems, particularly as these affect economic progress

ii. To review and monitor appropriate research programmes and mechanisms for the UK, taking full account of international co-operation, for example in the European Framework Programme and the World Ocean Circulation Experiment (WOCE).

iii. To review environment programmes of individual Government departments and agencies with a view to matching appropriately regulations and technology.

iv. To advise the Government on these aspects and any others which are relevant to environment issues.

WO353

CcDyP
cc HGuise

MR TURNBULL

c Ms Phippard
Mr Walker

26 January 1990

MEETING WITH SIR FRANCIS TOMBS - 31 January 1990

w Pris bof 26.1.90 -

I attach a brief which covers the topics which we know Sir Francis Tombs proposes to raise.

2. We have detailed replies from Departments on the suggestion that scientific advice in Whitehall is in decline, but I thought it more useful to annex only a brief summary of the key points about Departments mentioned in Sir Francis' letter.

JOHN FAIRCLOUGH
Chief Scientific Adviser

att:

BRIEF FOR THE PRIME MINISTER

MEETING WITH SIR FRANCIS TOMBS, CHAIRMAN, ACOST, 31 JANUARY 1990

Purpose of Meeting

1. Sir Francis wishes specifically to discuss the agenda for the ACOST meeting which the Prime Minister will attend on 14 March. His term of office ends in July and he also wishes to raise some other issues.

Agenda

2. 1. Agenda for ACOST meeting on 14 March

2. Size of ACOST

3. Work of ACOST

4. The role of Departmental Chief Scientific Advisers and Chief Scientist

Agenda for 14 March

3. Sir Francis wishes to offer the Prime Minister the choice of 3 topics from the following list of current ACOST studies:

i. The development of the Science Base since 1979.

ii. Adaptive biology.

iii. Advanced manufacturing technology.

iv. International cooperation.

4. Sir Francis will wish to explain these topics and his views on them. Main features are:

Science Base. Sir Francis considers that, contrary to some public criticism, the Science Base has done well financially in recent years. But problems remain in some areas and Sir Francis may wish to mention some doubts about the continuing validity of dual funding by the UFC and Research Councils, whose roles have become unclear.

Adaptive Biology is a very important aspect of Global Environmental Change. It is possible to develop animals and plants which remain productive in changed climatic conditions. ACOST are anxious that this basic science should not be overlooked in the current emphasis on Climatic Modelling.

Advanced Manufacturing Technology is an important factor in future industrial success. ACOST has been carrying out interesting work comparing UK capabilities with overseas competitors.

International Cooperation is of continuing and probably growing importance in relation to the Economic Community, Global Environmental Change and "Big Science".

Line to take

5. The Prime Minister may wish to listen to Sir Francis's explanations and suggestions. The science base and adaptive biology appear to be of high interest. The Prime Minister may consider that international cooperation is perhaps a more suitable subject than the more narrowly focused advanced manufacturing technology.

SIZE OF ACOST

6. The Prime Minister expressed a wish in May last year to reduce the size of ACOST and was advised that it should be possible to get down from 20 to 16 when Sir Francis completed his term of office. Sir Francis wishes to express his own views to the Prime Minister. Sir Robin Nicholson is aware of the issue but has insufficient knowledge of its current workload to offer a definite opinion.

7. Sir Francis is likely to argue that ACOST does not simply come together for infrequent full meetings. Much work is done in sub-committees and ad hoc groups. The burden of membership can be considerable for people who are, by definition, senior and very busy. A further factor is that attendance at full meetings averages 15.

Line to take

8. There is considerable force in Sir Francis's arguments but the Prime Minister may still think the essential work of ACOST could be done with fewer members.

THE FUTURE WORK OF ACOST

9. Sir Francis is likely to outline current developments, including particularly the establishment of an Environmental Sub-committee. He will ask the Prime Minister whether she has suggestions for particular topics or strategic emphases.

Line to take

10. The Prime Minister may wish to commend the general shape of the work of ACOST and to welcome the creation of the Environment Sub-committee. ACOST's speedy contribution to the work on the

European community Medium Term framework was particularly helpful. The current intensive work on environmental questions may lead to other cases where quick reactions are invited before policy is decided.

11. There is of course a continuing need to ensure that work is undertaken only if it is of high priority, other bodies have not got it in hand and ACOST can make a distinctive contribution.

DEPARTMENTAL CHIEF SCIENTIFIC ADVISORS AND CHIEF SCIENTIST

12. On 6 December, Sir Francis wrote to the prime Minister (Annex A) to express the concern of ACOST about what it sees as:

a. A decrease in scientific advice to government departments "based on experience external to the government service."

b. The down-grading of Chief Scientist posts.

c. The absence of Chief Scientist in the DES and Department of Transport.

d. Insufficient Brussels lobbying.

Background

13. Lord Rothchild's original report (1971) recommended that departments funding applied (not basic) research should have a "Chief Scientific Adviser" to act as "customer" for R&D and a "Chief Scientist" to act as "contractor". In practice, only the MOD and ODA have consistently followed this pattern although departments have all made arrangements to separate the customer and contractor roles under a single "Chief Scientist/Chief

Scientific Adviser". In recent years there has been particular emphasis on the operating divisions of departments acting as the customers with technical advice from the Chief Scientist or Adviser.

14. We agree with ACOST that the turning of government scientific establishments into Next Step Agencies makes it even more important for departments to be informed customers which requires a Chief Scientific Adviser with adequate expert staff.

15. Following Sir Francis's letter, enquiries have been made of all departments paying for significant research. The following main points have emerged:

i. It is impossible to track any general tendency to draw Chief Scientific Advisers from inside the public service or to down-grade them or both.

ii. Concern probably arose over the specific cases listed in the Tombs letter where special considerations have applied (Annex B).

iii. DES do not appoint a Chief Scientific Adviser because they are not concerned with applied research and the ABRC performs a broadly comparable task.

iv. The Transport Secretary is in course of appointing a part-time Adviser.

v. Departments, notably DTI and DOE, consider they lobby as vigorously in Brussels as is consistent with policy on expenditure.

16. Sir Francis is likely to avoid arguing specific debatable cases about Civil Service grading and to emphasise his own

judgement, supported by ACOST, that "the weight" of advice available to departments is less than it should be.

Line to take

17. The Prime Minister may wish to emphasise her recognition that it is important for Ministers to have high quality scientific advice informed by knowledge of the private sector and best practice there. She may wish particularly to agree that turning government scientific establishments into Next Step Agencies put a premium on departments being better informed customers.

18. She may wish to go on to say that she has looked closely at the present situation and its history. There has never been any consistant adoption of the pure "Rothschild" pattern of a Chief Scientific Adviser to serve the customer role and a Chief Scientist contractor. Different departments have adopted different patterns and considerable emphasis is placed on Advisory Committees and receiving advice from experts on specific topics.

19. There is no general downward trend in the grading or quality of those giving scientific advise and advisers are appointed after considering both inside and outside candidates.

20. Sir Francis referred to departments without Chief Scientists. The Prime Minister may wish to say that the DES is a special case because Sir David Philips and the ABRC perform a broadly comparable role. She is aware that Secretary of State for Energy is minded to appoint an adviser with expertise on environmental matters. The intention to make an early appointment of a Chief of Research and Development within the NHS and Department of Health has been anounced.

21. Sir Francis raised the particular question of the effectiveness of our lobbying in Brussels. This is a difficult issue because excessive activity can stoke the ambition of the Commission for ever larger programmes. But its importance is recognised and both DTI and DOE emphasise their commitment. The research councils are staffing an office there.

22. The Prime Minister may wish to conclude by saying she entirely agrees that the points raised by Sir Francis should be borne in mind by departments. His enquiry and the resulting approach to all permanent secretaries has served to remind them of the importance of high quality and broadly based scientific advice.

Cabinet Office
26.1.90

ANNEX B

SIGNIFICANT CHANGES IN DEPARTMENTAL ARRANGEMENTS FOR RECEIVING SCIENTIFIC ADVICE

PARTICULAR CASES RAISED BY ACOST

DEPARTMENT OF TRADE AND INDUSTRY

1. The present Chief Scientist, Dr Ron Coleman, is a Civil Servant with early experience of industry, but his two predecessors were from outside. He was appointed after internal and external candidates were considered.

DEPARTMENT OF ENVIRONMENT AND TRANSPORT

2. The combined departments used to have a Grade 2 Chief Scientist. Following the separation of the Departments, **The Department of the Environment** has a Grade 3 Chief Scientist, Dr David Fisk, who is very well-regarded and central to current work on Global Environmental Change.

3. **The Department of Transport** at present is advised by the Head of the Road Research Laboratory. The Secretary of State is in course of appointing an external adviser on polution matters.

DEPARTMENT OF ENERGY

4. The Department has a part-time Chief Scientific Adviser, who is also Chairman of the Advisory Council on Research and Development, Sir Richard Norman, at Grade 2 level. Some comments were made about the appointment of Dr David Evans as the Grade 3 "Head of Energy Technology and Chief Scientist". Although a career civil service administrator, he has a scientific PHd.

CABINET OFFICE

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Qd. 0150
File Ref: ST 117/1
ST 118/1

Seen by PS

Mr D Wilkinson
Head of Science Branch
Department of Education and Science
Elizabeth House
York Road
London SE1 7PH

24 January 1990

Dear David

Shifting the Boundary of the Dual Support System

Thank you for sending me your letter of 9 January with a copy of the Consultative Paper as issued.

2. We gave you our initial comments in my letter of 3 January. On further consideration, we wonder whether the process takes enough account of other developments and we would be grateful for further information before giving you a substantive response.

3. First, let me say that we agree with your support for the principle of the dual support system and we further agree that some changes are needed in its application and practice. We warmly welcome the separate identification of the elements of universities' block grants related to teaching and research criteria, soon to be implemented by the UFC. This will provide much needed clarity on university spend, which will in turn lead to a much clearer accounting system. This is all entirely consistent with the Strategy for the Science Base and with Mr Baker's speech.

4. We also welcome the consultation document as a step towards clarifying the dual support system boundary. We endorse the general definition of the purposes of research funded by UFC and by Research Councils that you give in paragraph 2 of your document but suggest that a fuller definition along the lines of the Merrison Report might be more helpful. This is because we see such a clear definition as the starting point for discussion of what funds should be transferred from UFC to Research Councils.

5. Using the Merrison definition, we see UFC support as providing a basic level of research activity, or 'seedcorn', for all university academic staff. As such, we expect it to be allocated according to criteria quite different from those used by Research Councils. Our overriding concern is that UFC research money should provide funds for the young scientist, novel/speculative ideas and transitions by scientists from one area of science to another. It should not duplicate or substitute for Research Council funding.

6. Our second concern relates to the more precise allocation of cost to particular projects. A transfer of money from UGC to Research Councils would achieve nothing if a substantial part of it were then merely apportioned as a fixed percentage to all research grants. We see the objective of the proposed transfer as being to relate payments more directly to costs and to ensure that these payments are targeted to those who carry out the research. We are therefore looking for a more transparent process for handling overheads.

7. There is a balance to be struck between comprehensive accounting and bureaucracy but we are aware that Universities are improving their cost accounting systems and it would be most helpful for us to know how far this has gone and what accounting practices we can expect universities to have. Presumably they have already developed systems to account for teaching and for research activities but we are uncertain of developments in more detailed attribution of overhead costs. If such systems are indeed in place or are being planned, this would have considerable implications for the assumptions we should base our substantive comments on.

8. It may well be best to discuss these issues, and to avoid a last minute rush would welcome an early meeting. Meanwhile, I am copying this letter on the E(ST)(O) net.

Yours,

C R WALKER

PRIME MINISTER

MEETING OF E(ST): 25 JANUARY

Tomorrow's meeting has only one item - the future of the Research Council system. The specific issue is what if anything should be done and said about a possible merger between the AFRC and the NERC.

You saw over the weekend the main paper by Mr. MacGregor (immediately below).

Other papers in the folder are:

- notes by John Fairclough and George Guise. These both argue on very similar lines for resisting John MacGregor's wish for early work limited to the specific issue of an AFRC/NERC merger. They want work done in slower time on more general reorganisation possibilities for the Research Councils;

- letter from the Chief Secretary, pointing to the potential costs of an AFRC/NERC merger;

- Cabinet Office handling brief.

The discussion should not take long. You will want to ensure that the meeting ends promptly by 1015. This is so that you can take John MacGregor to one side and have a word with him about the handling of the Chilver Report on teachers' pay. A speaking note from the Cabinet Office covering the points agreed at this evening's meeting is attached to this minute.

(PAUL GRAY)

24 January 1990

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PRIME MINISTER 23 January 1990

RESEARCH COUNCIL STRUCTURES

The current argument has been stimulated by the Morris Report which appeared last April following a remit from ABRC to examine the overlap between Research Councils in biological science. The team was chaired by Dick Morris, Chairman of Brown & Root and included three distinguished academics plus the research director of Amersham plc.

The report far exceeded its brief by presenting a penetrating analysis of the weaknesses throughout the whole Research Council system. This enraged many within academia and the Research Councils (Annex 2) and caused some embarrassment in parts of Whitehall. Its original recommendations have been thinned back and distorted into the clumsy proposal of John MacGregor's letter of December 21. This suggests announcing plans to examine a merger between AFRC and NERC. This is an oversimplification of one recommendation of the Morris report, and has produced much steam from Departments.

It is important to keep in sight the original Morris recommendations and to ensure that future proposals do not forget them. My first Annex summarises Morris's original ideas and my marginal comments were written at the time. In essence Morris recommends replacing the system of five Research Councils of vastly disproportionate scale with six organisations of re-allocated coverage. The approximate numbers are as follows:

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APPROXIMATE ANNUAL SPEND **£M (89/90)**

SERC 370/MRC 175/NERC 120/AFRC 70/ESRC 25 - Total 760

AS PROPOSED BY MORRIS

Biological and Environmental - Old AFRC plus biology from NERC and SERC	200
Astronomical & Nuclear Science - Now included in SERC	145
Physical Science - Phys, Chem, Geology, Maths ex SERC and NERC	110
Engineering & Technology - Now included in SERC	105
Medical Science (old MRC unchanged)	175
Economic & Social (Old ESRC unchanged)	25
	760

It is unfortunate that Morris describes these six entities as divisions of a single National Research Council. This has connotations of centralisation and enhanced bureaucratic control. It was initially criticised from all quarters, not only from vested interests like SERC but by normally sound people like Max Perutz. The latter referred to it in an article last year as the "Kremlinisation" of science!

In fact the proposal was to push the allocation mechanism down towards the level which would more readily recognise strong teams and good individuals. The top structure would have been thinner and cheaper than the present agglomeration of overheads. A Director General would chair an executive board comprising the heads of the six divisions plus non executive directors from academia and industry. Some of this has been retained by the new svelt ABRC concept although the latter's role remains advisory.

The Morris scheme was not perfect and you will see in the Annex some of my criticisms of his original ideas. However, it was a brave attempt to shake up the whole moribund Research Council structure and particularly to challenge the enormous monopoly of funds currently exercised by SERC. It would have separated both the applied work of the Engineering Board and the vast international ventures, such as CERN, from normal small scale physics and chemistry. These would therefore have received more protection from being squeezed by cost overruns elsewhere: a frequent complaint of those engaged in modest projects and indeed, yourself!

The other principal finding of Morris, namely that biology is literally evolving into many other branches of science is a direct response to the original remit. However, to oversimplify this into the straightforward merger of AFRC and NERC is both draconian and insufficient. Several Departments as well as John Fairclough oppose the identification of this single idea in any published response. Far better to support the honing down of ABRC into a more executive body under the full-time charge of David Phillips.

He should be given a private but clear remit to develop within

two years practical proposals for pushing down the allocation of research funds nearer to the workface. This may mean structual change along the Morris lines and it may need legislation, if such an unwieldy organisation as SERC is to be cut down to size.

In the meantime, since his executive team will include the Heads of the Councils, he should have great scope for banging these together. The turf consciousness and bickering of these warring science barons must stop and Philips should be told that is his immediate task!

Summary and Recommendations

1 The Morris Report has made many enemies and disturbed the menage between Whitehall and the universities. Despite its shortcomings (for example it does not address the question of UFC funding and some of its suggestions could be inflationary), the Report is a healthy piece of fresh thinking. It should stimulate Phillips and his new ABRC to come back with practical proposals.

2 No hint should be publicly given that the AFRC and the NERC might merge which was never the advice of the original Morris Report anyway. This would be a heavy handed way of dealing with those two councils, while encouraging SERC to believe it had escaped unscathed.

3 One long-term problem which needs work is the unwieldy size and remit of SERC. The Morris proposal to separate engineering and technology into one unit and costly international science into another makes a very good start.

GEORGE GUISE

ANNEX I - SUMMARY OF FIRST VERSION OF MORRIS REPORT

SUMMARY AND RECOMMENDATIONS

1. Research and training in the biological sciences is supported by the Agricultural and Food Research Council (AFRC), Natural Environment Research Council (NERC), Medical Research Council (MRC), and Science and Engineering Research Council (SERC). As the biological sciences have become more pervasive and mature, the boundaries between the responsibilities of these Councils in this area have become less clear-cut.

2. We thus undertook, on behalf of the Advisory Board for the Research Councils, a review of the disposition of responsibilities for biology between these four Councils. We also looked at arrangements for coordination and considered their effectiveness.

3. We were asked, in recommending any changes to Research Councils' responsibilities for the biological sciences, to consider the implications for fields related to the biological sciences. In any event, it is not possible, in present circumstances, to consider the biological sciences separately from the physical sciences with which they are integrated.

4. In our view, current arrangements for the support of the biological sciences do not provide for the flexibility and responsiveness which are so necessary, and coordination on matters of interest between two or more Councils needs to be more effective.

5. We advocate bringing together the biological sciences currently supported by AFRC, NERC and SERC into a "Biological and Environmental Sciences Division", one of six Divisions within a National Research Council. This Division would provide for the development of research and training in the non-medically orientated biological sciences, and the National Research Council, as a single organisation, would facilitate the close coordination of the biological sciences with the physical sciences and engineering, so important nowadays and for the future.

6. We thus propose a regrouping of the responsibilities of AFRC, NERC and SERC into the: Biology and Environmental Sciences Division, the Physical Sciences Division, the Engineering and Technology Division and the Astronomy and Nuclear Division. There would also be a Medical Sciences Division and an Economic and Social Sciences Division.

7. The activities of the National Research Council would be supervised by the Board of the National Research Council.

The Board would be both advisory and executive in function; it would replace the Advisory Board for the Research Councils.

8. There would be a Director-General of the National Research Council who would be the chief executive and Accounting Officer.

9. Our comments and recommendations thus have implications outside the biological area, indeed they affect substantially the arrangements through which Research Councils support civil science. In our view, the present system of completely independent Research Councils operating within relatively rigid boundaries set by their charters is no longer satisfactory.

10. Our main recommendations are as follows:

(1) We recommend that the Research Councils and the Advisory Board for the Research Councils be reconstituted as a single organisation to be known as the National Research Council (NRC). The NRC would take over all the resources and management responsibilities of the present Research Councils It would be an autonomous body, responsible and accountable to the Secretary of

It is thus apparent "Krenlinisation" into one body which Rothschild attacked. In practice specific funding allocation on the basis of personal & project merit would have been pushed downwards to the divisions - not centralised at the top.

State for Education and Science, and Parliament (Chapter 5, paragraph XX).

(2) We recommend that the NRC comprise the Board of the National Research Council (BNRC), together with six operating Divisions. The BNRC, which would replace the ABRC would oversee the activities of the NRC (Chapter 5, paragraph XX).

1 Biol & Environment
2 Physical Science
3 Astronomy & Mathem
4 Engineering & Technology
5 Medical
6 Economic & Social

(3) We recommend that there be a post of Director-General of the NRC. The post-holder would be chief executive and Accounting Officer for the NRC, and Chief Scientific Adviser to the Department of Education and Science (Chapter 5, paragraph XX).

(4) We recommend, as an immediate and interim measure, pending the formation of the NRC, that ABRC appoint two Planning Directors, one for the biological sciences and one for the physical sciences. These individuals would be responsible to the Chairman ABRC. They would develop proposals for the drawing together of the biological or physical elements in AFRC, NERC and SERC (Science Board), and also, if appropriate, MRC, to form the Biology and Environmental

Sciences Division, or the Physical Sciences Division. We would expect the Planning Directors to be experienced research managers (Chapter 5, paragraph XX).

(5) We recommend that UK Business Schools establish courses in the management of science and engineering research. We envisage that those taking up senior appointments in the management of Science Budget funded research would have attended such a course, and that eventually the attainment of a certain level of managerial competence would become a requirement for senior appointments (Chapter 5, paragraph XX).

Engineering "research can probably be managed in this sense. Basic Science certainly cannot. Who could have "managed" the work of Newton, Einstein or Francis Crick?

(6) We recommend a review, to include the research work of the Ministry of Agriculture, Fisheries and Food, the Department of Agriculture and Fisheries for Scotland, the Forestry Commission and the Nature Conservancy Council, to see whether any non-Research Council Government-funded research would benefit from integration into the National Research Council system we propose (Chapter 5, paragraph XX).

Yes, especially MAFF which is desperate for ways to reemploy all the people who were doing near market work!

(7) We recommend that part of the money transferred to the control of the Ministry of Agriculture Fisheries and Food as a consequence of Lord Rothschild's report ("A Framework for Government Research and Development, 1971") should be returned to AFRC. In so doing, we agree with the House of Lords Select Committee (Sub-Committee on Agricultural and Food Research) which argued that this money would be more productive as part of the AFRC budget, and that its return would recognise the increasing importance of strategic research as a proportion of total expenditure by the public sector on agriculture and food research (Chapter 5, paragraph XX).

Yes. AFRC spends its money far better than does MAFF.

(8) We recommend a thorough review of the operation of the customer-contractor arrangements set up following Lord Rothschild's report. Such arrangements, which need to be more stable and long-term, should incorporate the "General Research Surcharge". Also, commissioning funds, rather than the Science Budget, should bear a significant proportion of the costs of any Research Council restructuring consequent on a reduction in overall commissions (Chapter 5, paragraph XX).

This sounds inflationary and an encouragement to head costs.

11. We can think of no more apt summary of our views than is given in the following short extract from the Report of a Council for Scientific Policy Working Group, under the chairmanship of Lord, then Sir Frederick, Dainton "The Future of the Research Council System", 1971.

"... it is illogical on the one hand to assert the unity of science and fluidity of its internal boundaries and on the other to approve a system of completely independent Research Councils, each of which can only operate within relatively rigid boundaries set by its individual charter. The existence of these charters inevitably introduces a constraint which inhibits redeployment of effort and creates unnecessary demarcation problems".

ANNEX 2

THIS WEEK

Research councils face abolition threat

Andy Coghlan

THE LEADERS of Britain's research councils meet next week to discuss proposals for a revolution in the way that the country runs its science. Opposition to the plan is likely to be fierce, though the principal figures are keeping the details of their responses secret until after the meeting.

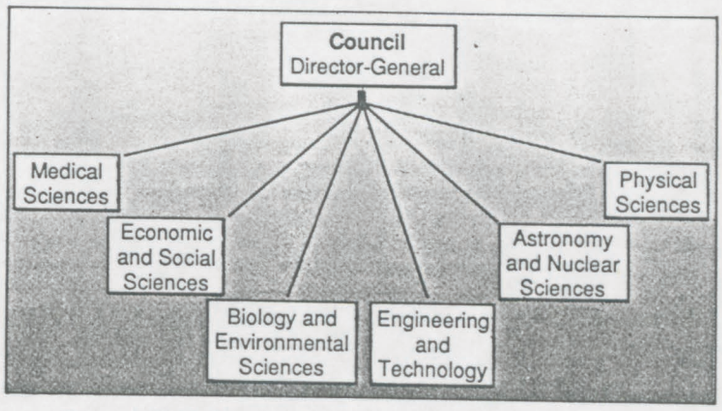
At present, five distinct councils share responsibility for managing British science. The Advisory Board for the Research Councils (ABRC), which called next week's meeting, oversees the activities of the five bodies. The board also advises the Secretary of State for Education and Science on how much money British science needs, and on how to distribute the sum that the government decides to give.

The new draft plan, commissioned by the ABRC, proposes sweeping away this structure completely. The upheaval would result in a single council absorbing all five existing councils and the ABRC. Six "semi-autonomous" divisions within the new council would be created by redistributing the resources of existing councils.

The aim of the shake-up would be to manage science more efficiently, to introduce a tighter management structure, to avoid duplication and to dismantle the institutional barriers to collaboration between existing councils.

Dick Morris, the chairman of Brown and Root, an engineering company, led the review group that produced the proposals. Initially, the ABRC directed the group to suggest ways of improving the management and organisation of the biological sciences but, as the group's inquiries proceeded, the authors decided to extend their recommendations to cover all British science.

Since April, when the board first received and circulated the new plan, more than 120 academic individuals and institutions have sent their responses to it to the ABRC's headquarters in the Department of Education and Science. The research councils refused to comment publicly in advance about the proposed changes, though the general tone of responses was disapproving.



One subdivided council would replace the five existing ones

The Science and Engineering Research Council, the biggest, regretted "errors of fact and misleading statements about SERC in the report". The council also described as "exaggerated" the review group's assertion that councils find it difficult to cooperate on science that cuts across boundaries between disciplines and councils. But the SERC says that it would be willing to work out the detailed structure for a "megacouncil" provided all the other existing councils accepted the strategy and agreed to form part of the National Research Council.

Of all the five research councils, the Agricultural and Food Research Council (AFRC) showed the least dissatisfaction. It supports a closer link between biological science and environmental science, the domain of the Natural Environment Research Council (NERC). "We're keen to see this sort of integration because biology is all-pervasive; you can't compartmentalise it," said a spokeswoman.

But, she said, the AFRC believes that a megacouncil might not be the only solution: "We might [otherwise] look to a merger with the NERC." The NERC refused to comment on the Morris report, although the council appears to have retreated from proposals it put forward in 1988 to merge with the AFRC to form a Natural Resources Research Council.

The Morris report says: "In evidence to us, the NERC did not seek major change in research council structures at this time. Its clear and distinct environmental role was emphasised as an essential and continuing component of the nation's response to a wide range of current and future environmental challenges."

The Medical Research Council (MRC) refused to say anything before next week's meeting (see Forum, this issue). The Morris report cites frictions that have arisen in the past in biotechnology where "initiatives of [the SERC's] Biotechnology Directorate have been repeatedly in conflict with MRC's view of its mission, particularly in areas of molecular biology and biology".

The Morris report asserts that individual research councils tend to react quickly and efficiently to new challenges—the MRC's response to AIDS, for example—but find it difficult to tackle problems jointly with other councils. The authors say that the SERC seems to be the most awkward partner.

A highly intricate job of redistributing resources among the six new divisions awaits administrators if the plan goes forward. According to the Morris report, the ABRC's first task would be to appoint two planning directors to carry out the task.

One director would draw together the biological elements of the AFRC, the NERC, the SERC and the MRC to form the division of Biology and Environmental Sciences. The other would form a Physical Sciences division from out of the same research councils. Both directors would be answerable to Sir David Phillips, the present chairman of the ABRC, until the National Research Council is fully constituted.

The NRC would be an autonomous body, accountable to the education secretary and Parliament. It would comprise 18 members: a part-time chairman; a director-general; the directors of the six new divisions; the Chief Scientist to the Cabinet Office; the chief executive of the Universities Funding Council; and eight independent members who would be drawn from industry, higher education and other parts of the scientific community.

The director-general would act as chief executive and accounting officer for the council. Directors of the six divisions, each on four-year contracts, would present their corporate plans to the council for approval. They would also administer the divisions.

This is the only kind of management structure, says the Morris report, that will succeed in a world where distinctions between disciplines are becoming increasingly blurred.

"We would want to see clear lines of management responsibility providing for considerable devolution of decision making. We expect such an arrangement also to yield significant cost savings by virtue of common administrative procedures and services, so providing for more research and training to be funded," it says.

The ABRC fails in this respect, it says. "The ABRC is not an executive body. [It] does have influence through its advice [to the secretary of state] on funding, but its terms of reference do not provide for it ▶

► to have the central management or executive role which is now sought." The authors find it "unsatisfactory that the ABRC does not bear management responsibility for the consequences for the research councils of its advice [to government]".

The Morris report rejects the American model, where the National Science Foundation administers everything except medicine, which is the province of the National Institutes of Health. The Morris report believes that this would still involve a body analogous to the ABRC to divide funds between the two, introducing an unnecessary tier of management.

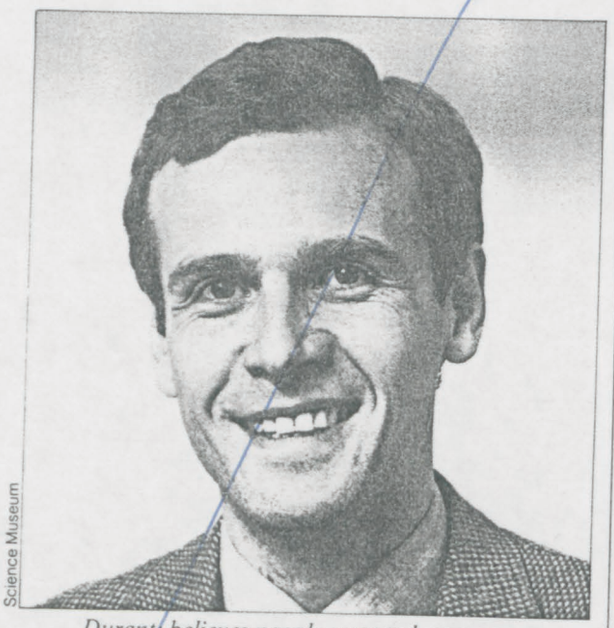
But the authors expect the NRC to benefit from links with counterparts in other European countries, as the need for collaboration grows.

One outstanding problem, if the proposals receive backing, is that each existing council has its own royal charter, which would have to be revoked before the new body came into being. This legal process could take up to two or three years. □

Survey reveals public ignorance of science

THE BRITISH and the Americans have a keener interest in science than they have in sport, films or politics, but they seldom possess a depth of knowledge that matches their curiosity on the subject. These findings appeared in last week's issue of *Nature*, which carried the results of a poll last summer of 2000 Britons and 2000 Americans.

The pollsters were led by John Durant of the Science Museum in London, who is Britain's first professor of the public understanding of science. They asked people which subjects they would prefer to read about, confronting them with a list of imaginary headlines for news stories. Consistently, and without prompting, respondents expressed more interest in science, particularly medicine, than any other topic.



Science Museum

Durant believes people want to learn more

Durant and his colleagues also asked people simple questions about science to measure their knowledge of scientific issues. Seventy per cent of the British participants judge natural vitamins to be more nutritious than synthetic ones. More than one-third think that they sprinkle their chips with calcium carbonate. Almost half of the respondents had no idea what DNA was.

Overall, the Americans had marginally better scores than the Britons. Forty-three per cent of Americans know that electrons are smaller than atoms, compared with 31 per cent of Britons. One-third of Britons know that it takes the Earth a year to orbit the Sun, compared with almost half of Americans.

If the results reflect wider trends, says Durant, then this suggests that most people misunderstand public issues that involve science. This in turn brings into question the quality of public debate and decision making in issues where science is pivotal.

For instance, half the respondents in Britain said that nuclear power stations cause acid rain. Only one-third thought the reverse. Half those questioned think that antibiotics kill viruses.

Perhaps predictably, says Durant, better-informed respondents tended to have a more positive attitude to science and to scientists. By and large, younger Britons know more about science than their elders; males usually know more than females; and middle-class people tend to know more about science than working-class people.

According to Durant "the results we have provided indicate that although the public is largely uninformed, it is also largely interested in science. This is surely a cause for optimism about the scope for improving the public understanding of science."

He added: "For science, technology and medicine, it appears that many people perceive a gap between themselves and a world of learning about which they would like to know more."

The pollsters also attempted to gauge the public's grasp of the fundamental rules of scientific investigation. "The results make rather gloomy reading for anyone who takes seriously the conventional, quasi-Popperian model of scientific method," say Durant and his colleagues.

The survey team asked the respondents simple questions designed to test how they would approach problems. One question, for example, gave respondents four options for organising the trial of a heart drug. Only one, the option of using a control group, was correct: 56 per cent of respondents chose it.

Responding to another question, only one-quarter of the subjects in Britain said that they "disagreed strongly" with the proposition that *all* of today's scientific theories will still be accepted in 100 years' time. Also, only 17 per cent of respondents "disagree strongly" that "new technology does not depend on basic scientific research". Almost 30 per cent "disagreed slightly" with this statement. □

Hair-raising fallout

A COMMISSION investigating why many children in the Estonian town of Sillamae have lost their hair has pointed to a dump of uranium waste as the most likely cause. Researchers had previously suggested that poisoning by thallium was responsible, in the wake of a similar incident in the Ukrainian town of Chernovpsy (This Week, 8 April).

At Sillamae, investigators have found uranium waste stored at a factory. Background levels of radiation measured by the Ministry of Health at the town show levels three or four times as high as normal, and higher still in some places. The local press is now calling for the removal of topsoil. The health ministry has allocated £60 million for environmental improvements.

Meanwhile, researchers have failed to track down the cause of what is still assumed to be thallium poisoning in Chernovpsy. More than 300 people are now affected. The government has set up a special toxicology research institute in the town and the World Health Organization has sent toxicologists.

Nobody is sure whether thallium is the real cause of the illness. The possibility of a viral infection is now being considered and there is concern about the high levels of dioxin found in nuts imported from Turkey and raisins from Afghanistan. Also, doctors have found that many of the children have concentrations of boron in their blood that are ten times as high as normal. □

Placental drug on trial

THE SOVIET authorities have granted a team of Georgian scientists the equivalent of a patent for a substance extracted from human placentas. The new product is called plaferon and is said to be an analogue of the group of proteins called interferons. (Interferons are produced by cells when a virus infects the cells; they inhibit cell growth). According to *Zarya Vostoka*, a daily newspaper in Tbilisi, the capital of Georgia, doctors have carried out several clinical trials of plaferon. These had promising results in treating disorders of the heart, nerves, eyes and urinary system, the newspaper claimed. Trials of plaferon for the treatment of viral hepatitis were particularly favourable, the report said. □

New moon for Neptune

THE VOYAGER 2 spacecraft has discovered a previously unknown moon orbiting the planet Neptune, bringing the planet's total number of satellites to three. Voyager will fly past Neptune on 25 August, and has been photographing the planet every three hours for the past month. In mid-June, one of the Voyager team, Stephen Sinnott, found a faint object near Neptune. Since then, he has worked out its orbit.

The new moon, with the temporary name 1989 N1, is between 200 and 600 kilometres in diameter, smaller than Neptune's known satellites, Triton and Nereid. It is also the closest to the planet, orbiting 117 500 kilometres from the centre of Neptune, about one-third the distance of Triton, the largest moon. □

All flights to US face checks

THE FEDERAL Aviation Administration (FAA) in the US is proposing that all baggage on flights to and from the US should be checked by an explosives detector. If the proposal becomes a regulation, airlines will have to install detectors in about 40 airports worldwide.

During the past four years, the FAA has spent $30 million on R&D for detecting explosives. The administration has looked at a range of equipment, and has chosen a device called a thermal neutron analysis system (TNA). The system bombards luggage with neutrons and detects the characteristic gamma-rays that explosives emit. If the proposed rule goes ahead, the airlines will have to buy the system. □

PRIME MINISTER

P 03610

THE FUTURE STRUCTURE OF THE RESEARCH COUNCIL SYSTEM
Memorandum by the Secretary of State for Education and Science
E(ST)(90)1

DECISIONS

1. E(ST) is to discuss Mr MacGregor's proposal for a study by the Advisory Board for the Research Councils (ABRC) of a merger between the Agricultural and Food Research Council (AFRC) and the National Environment Research Council (NERC).

2. You will wish to explore the arguments (some possible questions are set out below) and perhaps consider what the alternatives are: for instance -

i. an early study as proposed but with the Government's views explicitly reserved; or

ii. remitting the question to the new ABRC after 1 April.

BACKGROUND

3. In a minute to you of 21 December Mr MacGregor proposed:

i. reconstituting ABRC with a more explicit remit to improve coordination among the Research Councils;

ii. agreeing to advice from the ABRC that it should study the practical of closer association and possibly a merger of the AFRC & NERC.

The first of these was agreed and has been announced by Mr MacGregor. You, and some other colleagues, had reservations about the second: hence this discussion. Mr MacGregor wants to make an announcement on 29 or 30 January shortly before he next meets ABRC.

BBRC
Res Gr
AFRC.

MAIN ISSUES

Arguments for the merger

4. The main argument for the AFRC/NERC merger is that it makes no sense to separate responsibilities for the cultivated and natural environments between the two bodies. See especially paragraphs 10 and 11 of the officials' paper at Appendix A to E(ST)(90)1.

Arguments against the merger

5. You will however also want to explore these points:

i. Is there a risk that the merger would be more to the advantage of agricultural than environmental interests?

ii. Is there a risk that some of the work done by NERC would not fit well into the merged body? Mr Gray's minute of 2 January (Appendix B to paper) mentioned work on the oceans, satellite observation and computer climate models. Mr Hogg's letter of 16 January (Appendix H) mentioned geological surveying work and marine sciences research.

iii. Mr Gummer argues (Appendix F) that there is one item of AFRC's work - food research - which would not fit readily into the merged body.

iv. The AFRC and NERC are not the only Councils with an interest in biological research. The Medical Research Council (MRC) and the Science and Engineering Research Council (SERC) also have such an interest. Would a merger of AFRC and NERC be only a partial solution to the problem?

v. As the Chief Secretary pointed out in his letter of 19 January the merger would cost money which would come out of the Science Budget, reducing the scope for financing research. It would also divert effort.

The proposed ABRC study

6. Mr MacGregor proposes an immediate study by the ABRC, with the aim of a report by Easter. But the reconstitution of the ABRC, as already agreed, will take place on 1 April. You may wish to ask if it is wise for the work to be done through arrangements which are about to end and which the Government has accepted are defective.

The position of NERC

7. Mr MacGregor says that both AFRC and NERC would have to agree to the merger to avoid legislation. AFRC support it but NERC "will need to be persuaded". You may wish to ask if Mr MacGregor has any more news of NERC's attitude and if it is wise to press ahead against possible opposition from them.

Alternative possibilities

8. Other possibilities are:

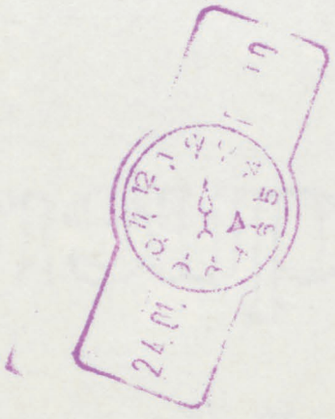
i. An immediate study as recommended by ABRC but with the Government's views reserved. Mr MacGregor's latest draft (at Appendix I) does not contain the endorsement of the principle of a merger which he earlier recommended. But he could go further and say explicitly that the Government has not yet reached a view on the principle.

ii. The question could be remitted to the new ABRC to consider after 1 April. Mr MacGregor hints at this in paragraph 6.i his paper. This would have the advantages of waiting until the new improved organisation comes into effect, and allowing a wider look at the question, covering also the position of the other Research Councils. If this possibility attracted you, you could ask Mr MacGregor to circulate further proposals on the timetable and scope of a study by the new ABRC.

HANDLING

9. The Secretary of State for Education and Science will wish to introduce his paper. Other Ministers with a Departmental interest are the Minister of Agriculture, the Secretary of State for Trade and Industry, the Chief Secretary, Treasury, the Foreign Secretary and the Minister of State, Department of the Environment (Mr Trippier). The Chief Scientific Adviser will also wish to comment.

R T J WILSON
Cabinet Office
January 23, 1990



WO3

PRIME MINISTER

23 January 1990

EST: THE FUTURE STRUCTURE OF THE RESEARCH COUNCIL SYSTEM

My letter of 9 January to the Permanent Secretary, DES is at Annex D to the Education Secretary's paper (E(ST)(90)1). You may, however, find it helpful if I set out what I see as the main considerations in the light of the further minuting and a discussion I have had with Sir David Phillips.

2. I think the major concern should be to get the reformed ABRC off to a good purposeful start. Its success will depend on the co-operation of the Heads of the independent Research Councils and their success in carrying the researchers with them. An urgent remit covering only part of the field would have a bad effect.

3. I would therefore prefer an outcome in which the new ABRC was not given a precise remit but was instructed to give careful consideration to enhance the cooperation between Councils, particularly in the core sciences and taking into account the difficulties identified in the Report prepared by Dick Morris which I understand you have seen. They should be invited to report back only when they lack power to make the changes thought necessary. At the end of the day legislation may be required to support a slimmer and less bureaucratic process. If this is the case, a maximum two-year time frame might be appropriate.

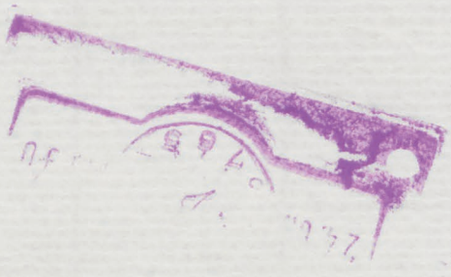
4. I should emphasise that while the new arrangements for the ABRC are imperfect, there is no reason why they cannot be made to work well. An excellent example which I hope will become a precedent is that research on global environmental change (covering

but not limited to climatic modelling) is being tackled by a management group, comprising the Research Councils, Meteorological Office and BNSC under the Chairmanship of an independent ABRC member and which will set priorities and decide funding.

6. Another advantage of the approach I prefer would allow more careful consideration of the Minister of Agriculture's recommendation that food research should be taken from the research councils and put in his department. While there may be a need for MAFF to have augmented resources to do work on standards, testing and safety, it would be wrong for them to try to fill the gap left by the removal of near-market research with the kind of basic and strategic research more appropriate to the Research Councils.

6. I am sending a copy of this minute to Sir Robin Butler.

JOHN FAIRCLOUGH
Chief Scientific Adviser



PRIME MINISTER

MEETING OF E(ST): 25 JANUARY

When you saw the latest note from John MacGregor earlier in the week about possible restructuring of the Research Councils, you asked for a discussion before any announcement was made. Meantime, you agreed that the slimming down and reconstitution of the ABRC should go ahead, and that has now been announced.

We have now arranged a meeting of E(ST) for next Thursday. The covering paper below from John MacGregor summarises the issues to be resolved (paragraph 6), and attaches as annexes the earlier exchanges.

I will arrange further briefing for next week.

PG

19 January 1990

jd c:est

dti

the department for Enterprise

The Hon. Douglas Hogg MP
Minister for Industry and Enterprise

Rt Hon John MacGregor OBE MP
Secretary of State for
Education and Science
Elizabeth House
York Road
LONDON
SE1 1PN

Department of
Trade and Industry

1-19 Victoria Street
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Enquiries
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Direct line 215 5147
Our ref
Your ref
Date 19 January 1990

Dear John

CO-ORDINATING COMMITTEE ON MARINE SCIENCE AND TECHNOLOGY - REPORT TO GOVERNMENT

Thank you for copying your letter of ~~19~~ December 1989 to Chris Patten setting out proposed actions for dealing with the Government response to this report. I am replying as I have responsibility for this subject within the Department.

I agree with your conclusions that whilst the CCMST have done a valuable job in drawing together the diverse strands of marine S&T and highligting a number of important issues; much of the argument to support its numerous recommendations lacks weight. Publishing the report now is much to be preferred to selective leaking and should help defuse possible lobbying activities whilst a constructive Government response is being prepared. As to co-ordinating this response I leave this for you to decide but you can be sure of the fullesst co-operation from my officials.

I am copying this letter to the recipients of yours.

Yours

DOUGLAS HOGG

ING1360

Sci-Tech : Budget. Pt10.

cst.ps/2nl15.1/lets

UNCLASSIFIED

CHIEF SECRETARY TO THE TREASURY

Treasury Chambers, Parliament Street, SW1P 3AG

The Rt Hon John MacGregor OBE MP
Secretary of State for Education and Science
Department of Education and Science
Elizabeth House
York Road
London
SE1 7PH

19th January 1990

Dear John

THE FUTURE STRUCTURE OF THE RESEARCH COUNCIL SYSTEM

Thank you for copying to me your minute to the Prime Minister of 21 December which proposed the merger of the AFRC and NERC and the establishment of a strengthened ABRC. I have also seen the Prime Minister's comments, recorded in her private secretary's letter of 2 January.

2 The merger of the AFRC and NERC would cost money which would come out of the Science budget, reducing the scope for financing research. I suggest the size of these costs, and the consequences for research funding, should be established before any decision is made.

3 I am content to see the ABRC made into a slimmer and more effective advisory body. But this proposal in no way diminishes the DES's responsibility for the allocation and use of Science budget funds nor the need for it to carry out the associated tasks of setting clear objectives, and monitoring and evaluating progress. While some progress has recently been made in this area - and I am pleased to note that at least one target for Research Council spending is included in the new public expenditure White Paper - much remains to be done before the position can be regarded as satisfactory.

4 You propose that the ABRC chairmanship be made into a full-time post and the secretariat strengthened. Provided the costs can be absorbed within your agreed running costs provision, I am content.

5 I am copying this letter to other members of E(ST), to Sir Robin Butler and to Sir John Fairclough.

NORMAN LAMONT

SCIENCE + TECH : Budget Patio

CONFIDENTIAL

10 DOWNING STREET

LONDON SW1A 2AA

From the Private Secretary

17 January 1990

Note

S/S Education rang me while this letter was in preparation. I told him the P.M. would be content for him to announce immediately the reconstitution of the AFRC. But he said that if AFRC/NERC could not be announced, he would prefer no announcement at all at this stage.

Dear John,

THE FUTURE STRUCTURE OF THE RESEARCH COUNCIL SYSTEM

Thank you for your letter of 16 January, enclosing a draft arranged parliamentary answer, which the Prime Minister has seen. Following my earlier letter to Stephen Crowne of 2 January, the Prime Minister has also seen the letter of 9 January from Sir John Fairclough to John Caines, the Minister of Agriculture's letter to your Secretary of State of 15 January and the Minister for Industry and Enterprise's letter of 16 January.

In the light of these further reactions the Prime Minister considers that there is a need to discuss the proposal for further work on a possible AFRC/NERC merger before any announcement about this is made.

I am copying this letter to the Private Secretaries to members of E(ST), Sonia Phippard (Cabinet Office) and to Sir John Fairclough.

Yours,

Paul

Paul Gray

John Ratcliff, Esq.,
Department of Education and Science.

CONFIDENTIAL

COPY.

ELIZABETH HOUSE
YORK ROAD
LONDON SE1 7PH
01-934 9000

Note
Archie taken on
in advance
fax copy.

Paul Gray Esq
Private Secretary
10 Downing Street
London SW1A 2AA

16 JAN 1990

PRC6
17/1

Dear Paul,

THE FUTURE STRUCTURE OF THE RESEARCH COUNCIL SYSTEM

We spoke about the announcement which my Secretary of State would like to make on Wednesday on this subject. I promised to send you for clearance a copy of the draft letter to Sir David Phillips, which my Secretary of State has proposed to Mr Patten and Mr Gummer should announce the Government's response to the ABRC's advice. It would form the basis for an arranged Parliamentary Question as in the draft attached.

You will have seen Mr Gummer's letter of 15 January which proposes that the letter be expanded to include a specific reference to the location of food research and the possibility of it reporting to his Department. Mr Patten has said that he is content with the draft, subject to some points on handling. In particular, he wishes to ensure that the outcome of the study is such as to avoid any damage to NERC's environmental mission.

My Secretary of State shares Mr Gummer's view about the need for the study to cover the location of food research, and has considered carefully in the light of his latest letter and of Mr Patten's comments whether any specific reference should be made to this issue in the letter to Sir David. His judgement is that it should not. He is very conscious of the Prime Minister's view reported in your letter of 2 January that a merger should only proceed if it can be demonstrated that the plan would work in detail and if it is agreed with all the relevant interests. Sir David's study will include the question of what is done with food research, but it would be a mistake to highlight this and this alone in any announcement at this stage.

The letter to Sir David Phillips was carefully drafted to leave open the full spectrum of possibilities from closer association to full merger. My Secretary of State would therefore prefer to retain the attached draft. But he does propose to speak to Sir David before the working group is set up to ensure that the study looks into the best location of food research.

He is also very keen to maintain good relations with the two Research Councils. The NERC full Council meets on Thursday, and he wishes as a courtesy to make an announcement the day before so that the Council is fully informed when it meets. I would therefore very much appreciate a response by 9am tomorrow, so that he can make the announcement as planned.

I am copying this letter to the Private Secretaries to the members of E(ST), Sonia Phippard (Cabinet Office) and to Sir John Fairclough.

Yours sincerely

John.

JOHN RATCLIFF
Private Secretary

DRAFT ARRANGED PARLIAMENTARY ANSWER

To ask the Secretary of State for Education and Science, when he expects to respond to the advice he has received from the Advisory Board for the Research Councils on the future structure of the Research Council system.

MR JOHN MACGREGOR

I have today written to Sir David Phillips, Chairman of the Advisory Board for the Research Councils, accepting the proposals put to me by the Board on the future structure of the Research Council System.

The text of my letter is as follows:

"Dear Sir David

FUTURE STRUCTURE OF THE RESEARCH COUNCIL SYSTEM

Thank you for your letters of 15 November and 1 December conveying the Board's advice about the future structure of the Research Council system.

The case which you put forward for reconstitution of the ABRC - as a smaller body with a more explicit remit to improve coordination and joint working among the Research Councils - is strong and convincing. The Government therefore intends to implement this recommendation with effect from 1 April. The terms of reference for the new ABRC will be those proposed in the annex to your advice. I am very pleased that you have accepted my invitation to become the first chairman of the new Board, and I hope to be able to announce its full membership within a few weeks.

I and my colleagues also welcome your proposal to establish a working group under ABRC auspices to examine the practicalities of achieving a closer association of the Agricultural and Food

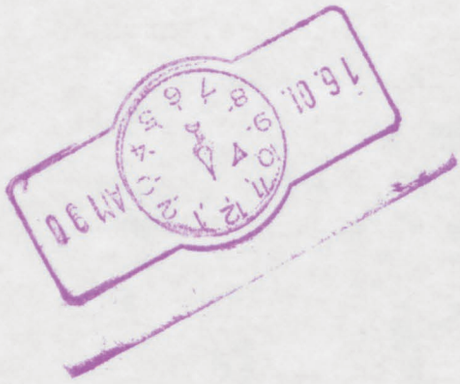
Research Council and the National Economic Research Council, and to consider further the possibility of a merger of the two Councils. I am sure that your group will want to consider carefully the implications across the full range of environment, agriculture and food research - addressing the need to sustain and develop physical science aspects of environmental research, and to build even more effective links with the research programmes sponsored by the Department of the Environment and the Ministry of Agriculture, Fisheries and Food, as well as to improve the coordination of terrestrial life science programmes.

Whilst scientific concerns should properly be to the fore, I trust that the working group will also look in detail at the appropriate form which closer association between the two Councils should take; at the stages through which, and on what timescale, this might progress towards full merger if that is judged to be beneficial; and at the changes in organisation and management structures that would be necessary along the way. Given the need to avoid prolonged uncertainty, I hope that a report on the group's work can be available by Easter.

I shall, naturally, be informing Parliament about the Government's conclusions on these matters and, given the wide interest in the scientific community, I am arranging for this letter and the Board's advice to be published."

Copies of this letter and of the Board's advice are being placed in the library.

SCI & TECH
Budget
Pt 9.



PRIME MINISTER

FUTURE STRUCTURE OF THE RESEARCH COUNCILS SYSTEM

Before Christmas you saw a note from John MacGregor (Flag A) proposing:

a) Reconstitution of the ABRC to a smaller body with a more explicit remit.

b) Signalling approval in principle of a merger between the AFRC and NERC, and announcing further work on this by a small group under David Phillips' chairmanship.

You commented on my minute at the time (Flag B) that you were content with the first proposal but had reservations on the second. I minuted out accordingly in my letter at Flag C.

Since then others have commented as follows:

- John Fairclough (Flag D) has added to your doubts about the possible AFRC/NERC merger. He argues that this is only part of the problem on research council demarcation and that these wider issues should be referred to the ABRC.

- John Gummer (Flag E) fully supports John MacGregor's original proposal but argues for special attention to be given to the future of AFRC'S research on food research.

- Douglas Hogg (Flag F) questions the case for an AFRC/NERC merger and suggests giving the new ABRC machinery a chance to work before considering major changes.

John MacGregor is however keen to press ahead with an announcement and his office have this evening sent me the further letter at Flag G. He ignores the point raised by John Fairclough

and the doubts from Douglas Hogg (although he may not have seen the latter). He wants to go ahead tomorrow with an arranged PQ answer, broadly on the lines of his original proposal. The reason for the haste is his wish that this should be done before the full NERC council meets on Thursday.

The terms of the proposed PQ answer are attached to the Flag G minute. In the light of your earlier comments the draft seems to me too warm towards the idea of a merger and I have marked some amendments in red to redress that. But in view of the comments from John Fairclough and Douglas Hogg you may alternatively want to consider resisting the idea of such an early announcement about the merger possibility and restricting this announcement simply to the reconstitution of the ABRC.

Conclusion

i) Content with the terms of the draft answer at Flag G subject to the amendments in red?

No

or

ii) Do you want to limit the present announcement to the reconstitution of the ABRC and suggest that this should be given time to settle in before further work on a possible AFRC/NERC merger is launched?

Yes - we clearly have different views from John Macgregor and we should discuss them before any decision is made

RACB.

Paul Gray
16 January 1990

c: research (MJ)

dti

the department for Enterprise

The Hon. Douglas Hogg MP
Minister for Industry and Enterprise

Rt Hon John MacGregor MP
Secretary of State
Department of Education and Science
Elizabeth House
York Road
LONDON SE1

Department of
Trade and Industry

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Telex 8811074/5 DTHQ G
Fax 01-222 2629

Direct line 215 5147
Our ref
Your ref
Date 16 January 1990

Dear John

FUTURE STRUCTURE OF THE RESEARCH COUNCIL SYSTEM

I have seen a copy of your minute to the Prime Minister of 21 December 1989, with proposals for the future development of the Research Council system.

I welcome the proposal to reconstitute and strengthen the ABRC, in order to promote improved co-ordination and joint working among the Research Councils, under a full-time Chairman.

I am less convinced about the advantages of a merger between the AFRC and NERC. One of the main reasons for the study carried out by Mr Morris, to which you refer was the need to improve co-ordination between the Research Councils in biologial sciences. A merger beween AFRC and NERC might divert attention from action to improve co-ordination between all four Research Councils involved in biological sciences. Perhaps we should give the new ABRC machinery a chance to see what it can achieve, before proceedings with major structural changes.

dti

the department for Enterprise

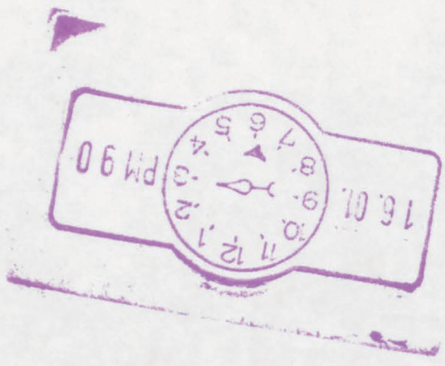
A merger with AFRC would in addition do little to help other areas of NERC's activity with which my Department is mainly concerned: the geological surveying work and marine sciences research.

I am sending copies of this minute to members of E(ST) to Sir Robin Butler and the Chief Scientific Adviser.

DOUGLAS HOGG

ING1327

Sci + TECH
Budget
Pt 9



6

ELIZABETH HOUSE
YORK ROAD
LONDON SE1 7PH
01-934 9000

Paul Gray Esq
Private Secretary
10 Downing Street
London SW1A 2AA

16 JAN 1990

Dear Paul,

THE FUTURE STRUCTURE OF THE RESEARCH COUNCIL SYSTEM

We spoke about the announcement which my Secretary of State would like to make on Wednesday on this subject. I promised to send you for clearance a copy of the draft letter to Sir David Phillips, which my Secretary of State has proposed to Mr Patten and Mr Gummer should announce the Government's response to the ABRC's advice. It would form the basis for an arranged Parliamentary Question as in the draft attached.

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My Secretary of State shares Mr Gummer's view about the need for the study to cover the location of food research, and has considered carefully in the light of his latest letter and of Mr Patten's comments whether any specific reference should be made to this issue in the letter to Sir David. His judgement is that it should not. He is very conscious of the Prime Minister's view reported in your letter of 2 January that a merger should only proceed if it can be demonstrated that the plan would work in detail and if it is agreed with all the relevant interests. Sir David's study will include the question of what is done with food research, but it would be a mistake to highlight this and this alone in any announcement at this stage.

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He is also very keen to maintain good relations with the two Research Councils. The NERC full Council meets on Thursday, and he wishes as a courtesy to make an announcement the day before so that the Council is fully informed when it meets. I would therefore very much appreciate a response by 9am tomorrow, so that he can make the announcement as planned.

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Yours sincerely

JOHN RATCLIFF
Private Secretary

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MR JOHN MACGREGOR

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I and my colleagues also [welcome] agree to your proposal to establish a working group under ABRC auspices to examine the practicalities of achieving a closer association of the Agricultural and Food

Research Council and the National Economic Research Council, and to consider further the possibility of a merger of the two Councils. I am sure that your group will want to consider carefully the implications across the full range of environment, agriculture and food research - addressing the need to sustain and develop physical science aspects of environmental research, and to build even more effective links with the research programmes sponsored by the Department of the Environment and the Ministry of Agriculture, Fisheries and Food, as well as to improve the coordination of terrestrial life science programmes.

Whilst scientific concerns should properly be to the fore, I trust that the working group will also look in detail at the appropriate form which closer association between the two Councils would take; at the stages through which, and on what timescale, this might progress towards full merger if that was judged to be beneficial; and at the changes in organisation and management structures that would be necessary along the way. Given the need to avoid prolonged uncertainty, I hope that a report on the group's work can be available by Easter.

I shall, naturally, be informing Parliament about the Government's conclusions on these matters and, given the wide interest in the scientific community, I am arranging for this letter and the Board's advice to be published."

Copies of this letter and of the Board's advice are being placed in the library.

The Govt will consider its reaction to such proposals in the light of this further work.

Ministry of Agriculture, Fisheries and Food
Whitehall Place, London SW1A 2HH

From the Minister

Rt Hon John MacGregor OBE MP
Secretary of State for Education and Science
Elizabeth House
York Road
London
SE1 7PH

15 January 1990

Dear Secretary of State

THE FUTURE STRUCTURE OF THE RESEARCH COUNCIL SYSTEM

Your minute of 21 December to the Prime Minister invited the agreement of colleagues in E(ST) to your proposals for reconstitution of the ABRC and for approval in principle of a merger between the AFRC and the NERC. I have subsequently seen Paul Gray's letter of 2 January recording the Prime Minister's views and the Chief Scientific Adviser's letter of 9 January to John Caines which suggests remitting the wider issue to the newly reformed ABRC rather than going ahead on the basis you have proposed.

I am content with the proposals for the ABRC given the safeguards, in paragraph 8c of your Department's paper, for the interests of Departments whose Chief Scientists would no longer be members.

As you say, we have discussed with Chris Patten, the proposal to merge the AFRC and the NERC. I accept in principle the case for a merger presented by the House of Lords and others. While I understand the difficulty Sir John Fairclough has with your proposal I am concerned that his approach might lead to yet another review of the whole structure and policy on R & D in the agriculture area. This would be unsettling for the staff and thus damaging to the science. I think it important to ensure that new arrangements are made known as soon as possible and that they are seen to maintain the commitment to research in agriculture and food currently exercised by the AFRC. I therefore agree that a study - restricted to the practicalities of a merger - would be the best way to take matters forward.

This study will need to consider, inter-alia, whether there are any parts of the current functions of the two councils which will not fit readily into the remit envisaged for the new council. I have made clear my view that it will prove necessary to separate out, and find an alternative location for, the AFRC's work on food research. I think that we should draw attention to this. If we agree at the outset that this will be necessary it would be desirable to pursue the arrangements for food research separately so as not to delay unnecessarily the study of arrangements for the AFRC-NERC merger as such. I would be happy for my officials to take the lead.

Whether the studies are separate or combined, I would wish my officials to be fully involved, particularly since we would need to resolve the financial responsibility for any new food body before changes can be announced. The best way of achieving this would be for Dr Peter Bunyan, my Chief Scientific Adviser, to be a member of Sir David Phillips' small group and I should be grateful if you would agree to this.

I confirm that I have agreed to Professor Stewart succeeding to the chairmanship of the AFRC as a short term measure pending decisions on the future of the council.

I agree that it would be sensible to look again at our response to the House of Lords Select Committee on Science and Technology, now that PES 1989 has been concluded and I am asking my officials to do this. I suggest we aim to deliver the response at the same time as any public announcement on an AFRC/NERC merger.

I have some small changes to suggest to your letter to Sir David Phillips and for convenience enclose a partial redraft.

I am sending copies of this letter to the Prime Minister, other members of E(ST), Sir Robin Butler and the Chief Scientific Adviser.

yours sincerely
Michael Hamson

JOHN GUMMER
(approved by the Minister
and signed in his absence)

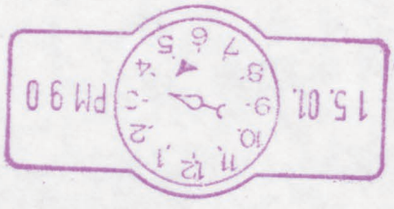
PARTIAL REDRAFT OF LETTER TO SIR DAVID PHILLIPS

..... possibility of a merger between the two Councils. I am sure your group will want to consider carefully the practical implications for environmental and agricultural science of a merger-addressing the need to sustain and develop physical science aspects of environmental research and to build even more effective links with the research programmes sponsored by DOE and MAFF, as well as to improve the co-ordination of terrestrial life science programmes. [The group will also need to look specifically at] [I am establishing a separate study to look specifically at] the possibility that food research, which would not fit naturally into the new studies we envisage, should report directly or indirectly to MAFF. For that reason and because of MAFF's major role in funding the work of AFRC John Gummer and I would like MAFF's Chief Scientific Adviser, [to chair a separate study, ~~and~~ as well as] to be a member of your group.

I trust that your group will look in detail at .....

p/phillips.dft

Sci+Tech: Budget. Pt 9



Foreign and Commonwealth Office

London SW1A 2AH

From The Minister of State

12 January 1990

Dear John,

Thank you for copying to Douglas Hurd your letter of 19 December to Chris Patten about the handling of the Government's response to the report of the Coordinating Committee on Marine Science & Technology. I am replying in his absence overseas. I have looked at this with a particular eye on the recommendation arising from Section 8.4 of the report.

I am content with your proposal to focus on the National Strategic Framework and the question of future coordination in this field, and with your recommendation that we should agree to early publication of the report. You will no doubt let us know in due course whether your Department or the Cabinet Office Science & Technology Secretariat will be coordinating the advice for Ministers on the response.

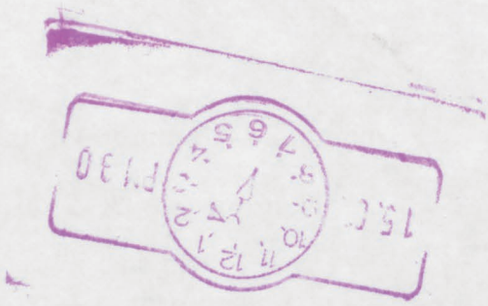
I am copying this letter to those who had copies of yours.

Yours ever,

THE LORD BRABAZON OF TARA

The Rt Hon John MacGregor OBE MP
Secretary of State for Education & Science
Elizabeth House
York Road
LONDON
SE1

SCI + TECH · Budget Pta.



CR.

file
(ACOST)

10 DOWNING STREET

LONDON SW1A 2AA

THE PRIME MINISTER

9 January 1989

Dear Sir Francis,

I am enclosing the Government response to ACOST's National Priorities Advice 1989 promised in my letter of 6 July 1989. The advice has made a valuable contribution to the Government's deliberations on science and technology, not least in informing the discussions in the 1989 Public Expenditure Survey.

I am grateful for all the studies and advice which ACOST has provided over the last year and look forward to participating in the Council meeting on 4 March.

Yours sincerely

Margaret Thatcher

Sir Francis Tombs.

GOVERNMENT RESPONSE TO ACOST'S ADVICE ON NATIONAL PRIORITIES FOR SCIENCE AND TECHNOLOGY: 1989

1. The Government are grateful for ACOST's Advice on National Priorities for Science and Technology: 1989 which helped to inform discussions in the PES round. The following paragraphs respond to ACOST's main recommendations.

GOVERNMENT S&T BUDGET

2. The Government demonstrated its commitment to maintaining and strengthening the science base by increasing the Science Budget planning figure in 1990/91 by 7%, giving a real terms increase of over 27% since 1979/80. This took account of earlier ACOST advice on priority areas for Government funding of Science and Technology. ACOST's 1989 Advice provided a valuable input into this year's PES discussions, following which provision for environmental research commissioned by the Department of the Environment is planned to increase by 21% between this year and 1992/93. The Advisory Board of Research Councils (ABRC)'s review of existing Interdisciplinary Research Centres (IRCs), welcomed by ACOST, has now been completed with ABRC stating that IRCs are appropriate in some fields and should become a normal part of the Research Councils' portfolio of support mechanisms for research. The Government and Research Councils stand ready to contribute to ACOST's new study of the science base. Government funding for S&T in future years is, of course, subject to annual negotiations in the PES rounds.

ENERGY R&D

3. The Government recognises that there may be changes in the overall amount and type of energy R&D undertaken following privatisation of the nationalised energy industries. The Department of Energy's own R&D programme is not designed to be comprehensive, but complements R&D done elsewhere, both in the public and private sectors. The Department is advised by the independent Advisory Council on R&D for Fuel and Power (ACORD) on

the size, balance, and composition of its own programme and those of the nationalised energy industries.

4. Privatised energy industries might place less emphasis on long-term R&D of a strategic nature, and ACORD will be considering what changes might come about to the amount and content of energy R&D following privatisation, and also what role the Department might play in ensuring that important national needs are met. The ACORD secretariat will keep ACOST informed of its deliberations on relevant issues.

5. Following previous ACOST advice and the decisions taken by Government in 1988 to scale down the fast reactor and fusion programmes, the AEA is beginning to reorganise itself, following a study by the business consultants, McKinsey. The reorganisation was welcomed by the Government in Ministerial statements before the Summer recess and the Authority has presented to the Chairman of ACOST its new business strategy designed to exploit its considerable strengths.

INDUSTRIAL R&D

6. ACOST recommends measures aimed at increasing the level of civil R&D in the UK (paragraphs 1, 13, and 14, recommendation 2). The Government welcomes the growth of 30% in real terms of industry's own funding of R&D in the four years to 1987, but agrees that a considerably higher level remains desirable if industry is to maintain and improve its competitive position. UK industry funds and performs R&D to about the same extent, as a percentage of GDP, as industry in USA and to a greater extent than in France or Italy. It still needs to improve, however to match Germany and Japan. The Government considers that its main role is to provide a favourable economic environment; for example, manufacturing profitability in 1988 was the highest since 1969. The Innovation Advisory Board, established by the Secretary of State for Trade and

Industry in the middle of last year, is giving priority to an examination of the ways in which the climate for innovation can be improved.

7. The first of ACOST's specific recommendations to increase R&D is for an extension to the Consultancy Initiatives to cover the formulation and management of R&D programmes. The Consultancy Initiatives are reviewed regularly. Following the latest of these, DTI has recently made changes (see paragraph 17 below); ACOST's proposals will be considered during the next review.

8. ACOST's recommendation 2 ii. is that steps should be taken to increase the awareness of the importance of R&D to smaller companies which carry out little or no R&D. While some of the DTI supported collaborative research programmes are aimed at small and medium-sized enterprises (SMEs), the technology transfer programmes are almost entirely aimed at SMEs.

9. Government's view on recommendation 2 iii., concerning the recent decision by the Accountancy Standards Committee to require disclosure of R&D in company accounts, is that any consideration of changes should await experience of how the new arrangements work in practice.

EDUCATION AND TRAINING

10. ACOST recommends that the Department of Education and Science (DES) and others give renewed impetus to measures to increase the number of science and mathematics teachers in British schools and expresses concern about the availability of young people trained in science and engineering (paragraph 2, recommendation 3). The Government shares the Council's view about the importance of increasing the number of science and mathematics teachers. DES has already put a number of measures in hand and will be reinforcing and extending these (eg the Research Councils' recent increases in the value and number of postgraduate studentships). The Government looks forward to receiving the results of ACOST's study,

particularly their findings on the effectiveness of current initiatives. The Department set out its thinking on the problems of teacher supply in its memorandum to the Education, Science and Arts Select Committee in November 1988, and, more recently, in the previous Secretary of State's Inaugural IBM Education Lecture on 23 May 1989.

11. In recent years the introduction of the General Certificate of Secondary Education (GCSE) and the Technical and Vocational Educational Initiative (TVEI) have increased the numbers of young people studying balanced science in schools. The National Curriculum which is now being introduced will ensure that all pupils study science and technology from 5 to 16, and all pupils will be expected to take science to GCSE. Improved continuity of experience from 5 to 16, and attainment targets which give all pupils something to aim at, will raise standards significantly and improve the scientific and technological knowledge-base of the nation. Many more pupils will have the qualifications to pursue AS and A level studies or other post-16 studies in science and technology. The Government aim is for all young people who do not stay in full-time education to have the opportunity to achieve a recognised vocational qualification. The Government attaches importance to improved advice for young people on post-16 study and careers, and local education authorities must commit themselves to this as part of TVEI.

ANNUAL REVIEW

12. ACOST's fourth recommendation is for more analysis in the Annual Review on spend by technologies and on qualified scientific and engineering manpower - and for a more rapid processing of comprehensive information on industrial R&D. Analyses based on technology classifications have proved to be unreliable because of the effects of personal judgements in classification; this classification becomes even less trustworthy as Government R&D funding is focussed more towards basic science. There are no plans to reinstate it. The 1989 Annual Review contained, in response to

ACOST and other requests, data on scientific and engineering manpower. Manpower data will continue to be given in future years. However, as the provision of greater detail on manpower in industry and greater emphasis on small firms would increase the form-filling burden on firms, particularly small businesses, very strong justification would be needed for this. The delay in publishing the industrial R&D sample survey results is due mainly to the slow return of forms from industry. Compared with the sample survey, the quadriennial full survey is more complex and covers many more businesses. It therefore takes longer for industry to respond and the returns themselves require careful checking.

DTI

13. ACOST advises that DTI should take a less detached role in technological leadership, with more strategic thinking on longer term technological developments (paragraph 6, recommendation 5). DTI agrees that such strategic thinking is important, but believes that the lead should be provided by those who carry out research, develop and exploit technology. The Department therefore draws heavily on advice from Research Councils and industry in formulating priorities for research programmes - for example, the four main areas of technology supported through LINK are biotechnology, electronics, advanced materials and advanced manufacturing. DTI also values the strategic advice of ACOST and CEST.

14. The Council suggests that DTI laboratories are finding it difficult to fulfil a useful role (paragraph 9, recommendation 5). Following a review last year, clear remits were announced for the Research Establishments; their principal function is to support Departments in the development and implementation of their policies. Much of the effort is devoted to the National Measurement System, with substantial resources also in support of protection of the environment, public health and revenue collecting activities. The move of all the DTI Research Establishments to Executive Agency status will further strengthen and clarify their

roles. Not only will each agency respond to demands from DTI and other Departmental customers, but each will have a corporate plan prepared by the Chief Executive, with advice from a Steering Board whose membership includes industrialists and business people.

LINK AND EUREKA

15. The Government welcomes ACOST's strong support for LINK and EUREKA (paragraphs 7, 8 and 26, recommendations 6 and 9) - indeed these are the two highest priorities within the DTI's collaborative research portfolio and it is planned that they will account for a rapidly increasing share of it. DTI and SERC were the first major movers in LINK and other Departments and Research Councils are now becoming more involved; a good number of programmes have been launched and many more projects are coming through. The Government believes that it is yet too early for the review of LINK proposed by ACOST.

16. Recommendation 9 deals with ACOST's valuable proposals on EUREKA which have been made separately to DTI. DTI has already implemented some of the proposals and the EUREKA Office has been strengthened; others are being reviewed prior to providing ACOST with a carefully considered response.

SMALL FIRMS

17. The Council's recommendations (paragraphs 16, 17 and 18, recommendation 7) on small firms are drawn from the wider recommendations in their major report of July 1989 'Overcoming Barriers to Growth in Smaller Firms'. The Government has responded separately on that report. However DTI has already made some changes to the Consultancy Initiatives which go some way to meeting the Council's recommendation for a technology audit. The terms of reference for a standard 5-day consultancy on manufacturing now provide for an assessment of a firm's current level of technology, including recommendations on improvements in technology to meet business goals. Also under a Design consultancy a firm can obtain

an assessment of its products and technology, and advice on improvements (including recommendations on intellectual property and technology licensing).

GLOBAL ENVIRONMENTAL RESEARCH (GER)

18. The Government agrees with ACOST's recommendation (8) for an increase in support for fundamental science in GER. As well as chemical and biological aspects, continued emphasis is needed on physical processes which are vital to an understanding of both atmosphere and ocean. This year's PES round has increased provision to sustain scientific research programmes while meeting the construction costs of the Antarctic research and logistics vessel RRS James Clark Ross; and for a UK contribution to ERS-2, for an Along Track Scanning Radiometer to measure surface ocean temperature. The Prime Minister, in her speech to the UN General Assembly on 8 November highlighted the importance of GER work and of the major contribution the UK could make through the Climate Research Centre to be set up at the Meteorological Office, Bracknell. A significant part of the increase in funding for environmental R&D mentioned in paragraph 2 above will be used to fund this work.

19. ACOST recommends a directorate to 'task force' UK participation in domestic and international research - and the establishment of a greenhouse gases review group (recommendation 8). Government sponsored GER R&D involves the Research Councils and spans several Departments. The Government does not accept the proposal for a task force, but is aware of the need for proper coordination and is currently considering the most effective mechanisms for guiding and informing all aspects, including the economic and social implications of global environment change.

20. The Government welcomes ACOST's recognition of the private sector role in GER (paragraph 20). Work in industry to devise environment-friendly substitutes for a number of materials and

industrial processes should lead to big business in the future. This very much follows the lines of the exploitable science discussed in paragraphs 22-24 of the Advice.

DEPARTMENT OF HEALTH

21. ACOST recommend (paragraph 29, recommendation 10) that the Department of Health should include industry representatives on its R&D funding committees as far as possible and that it should study further the opportunities in the primary health sector. The latter is given high priority in the R&D support by the Department of Health. The Department has invited both ABHI and BTG to sit on the R&D Co-ordinating Group on Medical Equipment. The role of this Group is being reviewed; its co-ordinating activities will be sharpened.

FCS/90/001

SECRETARY OF STATE FOR EDUCATION AND SCIENCE

The Future Structure of the Research Council System

1. I have seen a copy of your minute of 21 December to the Prime Minister outlining your proposals on restructuring the Research Council System.

2. International collaboration is now more important than ever, not least because the cost of many scientific facilities makes such collaboration desirable. I hope that this will be taken into account when deciding upon the structure and membership of the new ARBC and in considering whether a merger between the AFRC and the NERC would be beneficial.

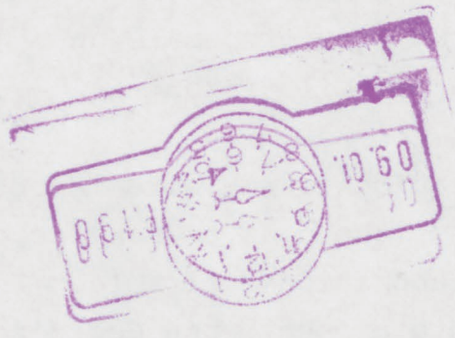
3. I am copying this minute to members of E(ST), Sir Robin Butler, and the Chief Scientific Adviser.

DH.

(DOUGLAS HURD)

Foreign and Commonwealth Office
9 January 1990

SCI + TECH: Budget PTA



cc PM

MAFF

Ministry of Agriculture, Fisheries and Food
Whitehall Place, London SW1A 2HH

From the Minister

The Rt Hon John MacGregor OBE MP
Secretary of State for Education and Science
Department of Education and Science
Elizabeth House
York Road
London SE1 7PH

NBPM
At this stage.
BRC 9/1

7 January 1990

Dear Secretary of State

REPORT OF CO-ORDINATING COMMITTEE ON MARINE SCIENCE AND TECHNOLOGY

Thank you for copying to me your letter of ~~19~~ December to Chris Patten about the report of the Co-ordinating Committee on Marine Science and Technology.

I agree that the quality of this report is uneven. The Committee have covered a very large amount of ground; and, while they seem to have identified sensible objectives for a national strategy for marine science and technology and a reasonable set of major research areas, not all of their report is equally well thought through or justified. However, on balance, I accept that it would be best to agree to the report being published despite its weaknesses.

I do not have strong views about how the preparation of the Government response to this report should be coordinated. Whatever arrangements are adopted, I will of course want my officials to be fully involved in the necessary interdepartmental discussions.

I am copying this letter to those who had copies of yours.

Yours sincerely

A J Lebrecht

JOHN GUMMER
(approved by the Minister and signed in his absence)

SCITECH : Budget Prg.

CABINET OFFICE

70 Whitehall London SW1A 2AS Telephone 01-270 0259

From Sir John Fairclough FEng
Chief Scientific Adviser

W0329

John Caines Esq CB
Department of Education and Science
Elizabeth House
York Road
London SE1 7PH

9 January 1990

Dear John,

THE FUTURE STRUCTURE OF THE RESEARCH COUNCIL SYSTEM

I was of course interested to see your Secretary of State's minute of 21 December to the Prime Minister and the No 10 reply of 2 January.

As you know, I welcome the proposed changes to ABRC and the scope they create for greater cooperation between HORCs. I think it will be important to establish from the outset that there will be a formal review of how well the new procedures work in, say, two years. A further strengthened but still small ABRC Secretariat will be vital. The HORCs would no doubt be prepared to second further staff in the light of their own increased role in the machinery. One area where I think an early view needs to be taken is the establishment of compatible if not identical information systems for the Research Councils.

I have to say that I very much agree with the Prime Minister's approach on a possible AFRC/NERC merger. I recognise that there are strong arguments for reorganisation in the environmental area, but I am convinced that the problem you are seeking to address does not lie neatly within the present boundaries of the two Research Councils. Further thought needs to be given to the objections to be pursued and the aims of any new body. If I had to characterise the problem, it would be the difficult interface between the three Research Councils with clear missions and the less focused, more basic role of SERC. I would suggest that this wider issue should be referred immediately to the reformed ABRC where I would hope to contribute as an assessor. It would in my view be better to

continue with the present Research Council structure under a more effective ABRC than an inevitably burdensome and controversial step which did not get to the core of the problem.

I am copying this letter to Robin Butler, Paul Gray and the Permanent Secretaries of Departments whose Ministers are members of EST.

Yours sincerely,

John

JOHN FAIRCLOUGH

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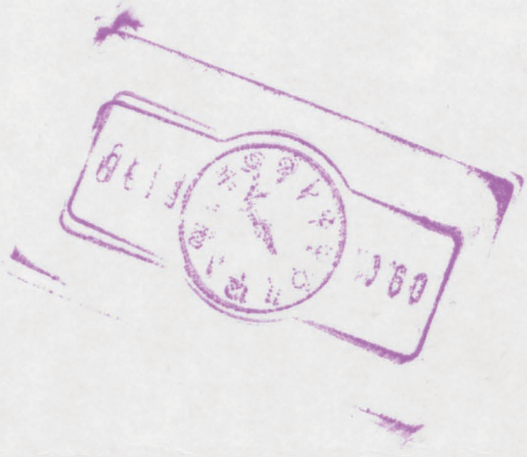


SECRETARY OF STATE FOR THE ENVIRONMENT

2 MARSHAM STREET
LONDON SW1P 3EB
01-276 3000

My ref:

Your ref:

Roy Walker Esq
Cabinet Office
70 Whitehall
LONDON
SW1A 2AS

8 January 1990

Dear Roy

ACOST ADVICE ON NATIONAL PRIORITIES: GOVERNMENT RESPONSE

The Secretary of State for the Environment is content with the draft response circulated under your letter of 18 December, save for the need for some clarification to the second sentence of the second paragraph of the draft. The planned increase in provision for environmental research referred to, relates specifically to the DOE's planned increase and I suggest this should be made clear. This can be achieved by inserting "commissioned by the Department of the Environment" after "environmental research" in the seventh line of the second paragraph.

I am copying this letter to the Private Secretaries of other members of E(ST), who I suggest can contact you if they have any difficulty with my suggested insertion.

Yours sincerely

Roger Bright

R BRIGHT
Private Secretary

SECRETARY OF STATE FOR THE ENVIRONMENT

2 MARSHAM STREET
LONDON SW1P 3EB
01-276 3000

My ref:

Your ref:

Roy Walker Esq
Cabinet Office
70 Whitehall
LONDON
SW1A 2AS

8 January 1990

Dear Roy

ACOST ADVICE ON NATIONAL PRIORITIES: GOVERNMENT RESPONSE

The Secretary of State for the Environment is content with the draft response circulated under your letter of 18 December, save for the need for some clarification to the second sentence of the second paragraph of the draft. The planned increase in provision for environmental research referred to, relates specifically to the DOE's planned increase and I suggest this should be made clear. This can be achieved by inserting "commissioned by the Department of the Environment" after "environmental research" in the seventh line of the second paragraph.

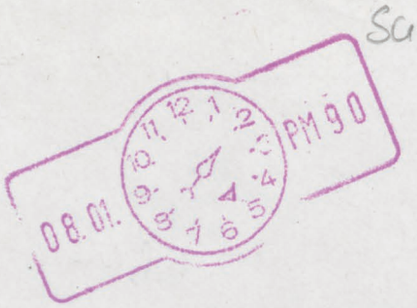
I am copying this letter to the Private Secretaries of other members of E(ST), who I suggest can contact you if they have any difficulty with my suggested insertion.

Yours sincerely

Roger Bright

R BRIGHT
Private Secretary

SG + TGCH : Budget FY9



THE RT HON JOHN WAKEHAM MP

Department of Energy
1 Palace Street
London SW1E 5HE

01 238 3290

The Rt Hon John MacGregor OBE MP
Secretary of State for Education
and Science
Elizabeth House
York Road
LONDON
SE1 1PH

8 January 1990

Dear John

CO-ORDINATING COMMITTEE ON MARINE SCIENCE AND TECHNOLOGY - REPORT TO GOVERNMENT

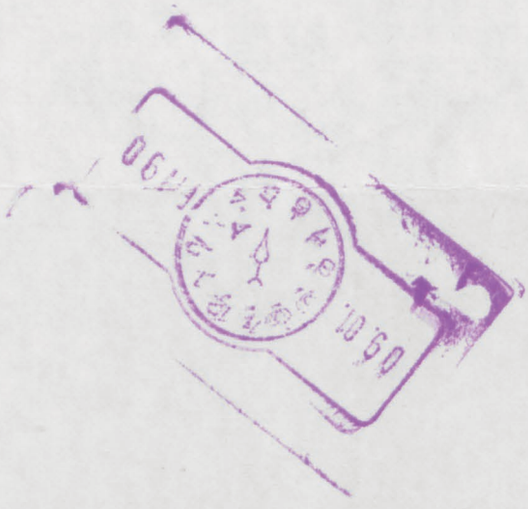
Thank you for copying to me your letter of 19 December to Christopher Patten.

I am content with your proposals that the report of CCMST should be published and that the government response should focus on the Strategic Framework identified by the Committee, rather than on the mass of detail contained in the main report. My Department will play an active role in the preparation of our response. I believe that oil and gas-related technology, and the industrial capability that goes with it, are crucial to the future of marine technology in this country. Oil companies, and my Department's Offshore Supplies Office, are already engaged in many of the key areas of technology identified in the Strategic Framework.

I am copying this letter to the recipients of yours.

Yours ever

JOHN WAKEHAM



dti

the department for Enterprise

cc PS

The Rt. Hon. Nicholas Ridley MP
Secretary of State for Trade and Industry

. C R Walker Esq
Cabinet Office
70 Whitehall
London
SW1A 2AS

Department of Trade and Industry

1-19 Victoria Street
London SW1H 0ET

Enquiries
01-215 5000

Telex 8811074/5 DTHQ G
Fax 01-222 2629

MBPM

RRC6

9/1

Direct line 215 4442
Our ref NP1AHX
Your ref
Date 8 January 1990

Dear Mr Walker,

ACOST ADVICE ON NATIONAL PRIORITIES: GOVERNMENT RESPONSE

Thank you for your letter of ~~19~~ December attaching a draft Government response to ACOST's National Priorities Advice 1989. My Secretary of State is content with this draft.

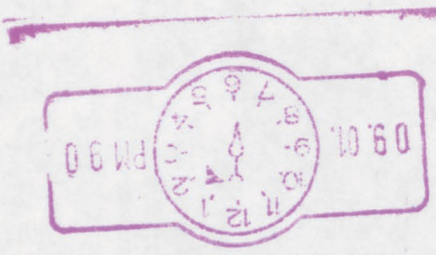
Put with PS

I am copying this letter to the Private Secretaries of other members of E(ST).

Yours
Rosalind Cole

ROSALIND COLE
Private Secretary

SCI + TECH : Budget PTQ



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FROM: MR R WALKER
DATE: 8 JANUARY 1990

MR PAUL GRAY

GOVERNMENT RESPONSE TO ACOST'S NATIONAL PRIORITIES ADVICE 1989

I enclose the proposed Government Response to ACOST's National Priorities Advice for the Prime Minister to send to Sir Francis Tombs; it has been cleared by E(ST) Ministers.

2. You may wish to add to the draft a reference to Tombs's peerage.

3. We briefly discussed the need for Sir Francis to receive the Response as soon as possible because ACOST is scheduled to discuss it at a meeting on 16 January.

4. I am copying this letter to Richard Wilson and Sonia Phippard.

ROY WALKER
S&T Secretariat
Cabinet Office

c:\ACOST

DRAFT LETTER FROM THE PRIME MINISTER TO SIR FRANCIS TOMBS

I am enclosing the Government Response to ACOST's National Priorities Advice 1989 promised in my letter of 6 July 1989. The Advice has made a valuable contribution to the Government's deliberations on science and technology, not least in informing the discussions in the 1989 Public Expenditure Survey.

I am grateful for all the studies and advice which ACOST has provided over the last year and look forward to participating in the Council meeting on 4 March.

ELIZABETH HOUSE
YORK ROAD
LONDON SE1 7PH
01-934 9000

C R Walker Esq
Cabinet Office
70 Whitehall
London
SW1A 2AS

- 2 JAN 1990

Dear Roy

Thank you for your letter of 18 December about the Government Response to ACOST's National Priorities Advice 1989.

The Secretary of State has seen the draft Response and is content subject to the following two points.

First, paragraph 2 does not quite reflect the ABRC's views on IRCs. Lines 11 and 12 should be amended as follows:

> "with ABRC stating that IRCs are appropriate in some fields and should become a normal part of the Research Councils' portfolio of support mechanisms for research. The Government..."

Secondly, we understand that the figure in paragraph 2 line 8 for an increase in spending on environmental research relates only to research funded by the Department of the Environment. You may wish to amend the draft to make this clear.

Copies of this letter go to the Private Secretaries of other members of E(ST).

Yours sincerely

Stephen Crowne

S CROWNE
Private Secretary

SCIENCE + TECH. Budget

10 DOWNING STREET

LONDON SW1A 2AA

From the Private Secretary

2 January 1990

Dear Stephen,

THE FUTURE STRUCTURE OF THE RESEARCH COUNCIL SYSTEM

The Prime Minister was grateful for your Secretary of State's minute of 21 December, together with the attached paper by officials.

The Prime Minister is content with the proposal to reconstitute the ABRC into a body with fewer members, a full-time Chairman, a strengthened secretariat and a more explicit remit to improve co-ordination and joint working among the various Research Councils. She is also content for Sir David Phillips to be appointed the full-time Chairman.

As regards the possibility of a merger between the AFRC and the NERC, the Prime Minister has noted from the paper by officials that members of the NERC remain to be persuaded of the benefits of this approach. The Prime Minister feels that a merger could be more to the advantage of the agricultural interests than various aspects of the NERC's work, such as that on oceans, satellite observation and computer climate models. While she is content for the proposed detailed work on the possibility of a merger to be carried out by a small group under Sir David Phillips' Chairmanship, she considers that a merger should only proceed if it can be demonstrated that the plan would work in detail and it is agreed with all the relevant interests.

I am copying this letter to the Private Secretaries to the members of E(ST), Sonia Phippard (Cabinet Office) and to Sir John Fairclough.

Yours,
Paul

PAUL GRAY

Stephen Crowne, Esq.,
Department of Education and Science.

PART 9 ends:-

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PART 10 begins:-

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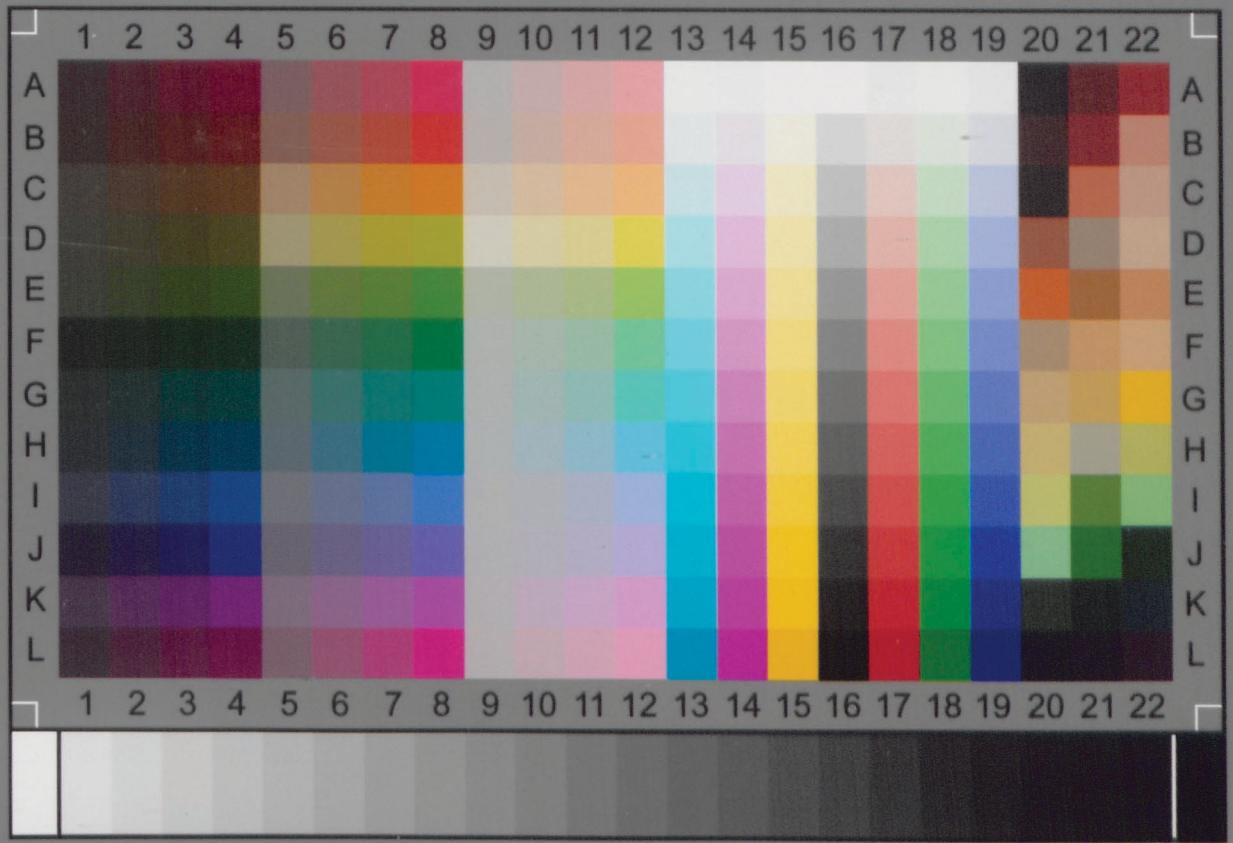

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