PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

The Florey Lecture, 1990: How is the Cell Division Cycle Regulated?

Paul Nurse

Phil. Trans. R. Soc. Lond. B 1991 **332**, 271-276
doi: 10.1098/rstb.1991.0055

The Florey Lecture, 1990

How is the cell division cycle regulated?

PAUL NURSE

ICRF Cell Cycle Group, Department of Biochemistry, University of Oxford, South Parks Road, Oxford OX1 3QU, U.K.

CONTENTS

SUMMARY

It is argued in this lecture that in most eukaryotic cells onset of mitosis is coupled to attainment of a critical cell mass and to completion of the previous S-phase. In fission yeast these controls operate through a regulatory gene network that activates the $p34^{cdc2}$ protein kinase at mitosis. This is brought about by dephosphorylation of a tyrosine residue located in the ATP binding site of the kinase. The $p34^{cdc2}$ protein kinase is also important for regulating the onset of mitosis in vertebrate cells suggesting that there is a universal control regulating mitosis in all eukaryotic cells.

1. INTRODUCTION

This lecture is dedicated to the memory of Howard Florey, and the intention of its founders was that it should be on a topic that would have been of interest to him. His work was concerned mainly with the study of microorganisms in relation to infectious disease, a major medical problem of his time. It is my hope that he would have had some interest in this lecture, which describes the use of microorganisms for study of the cell cycle a phenomenon of relevance to cancer, a major medical problem of today.

The title of this lecture is 'How is the cell division cycle regulated?' The cell division cycle is defined as the period between the birth of a growing cell and its subsequent division (Mitchison 1971). It has been clear since the mid-nineteenth century, soon after the origin of the cell theory, that the control of cell division is a fundamental biological problem of universal significance to all organisms. Recognition of this universality can be seen in a quotation from Butschli written in 1876:

> In both the rejuvenated infusorisan and the fertilized egg-cell we see the onset of an energetic multiplication by cell-division which leads in the one case to the formation of a multicellular organism and in the other to a series of cell generations.
>
> Translation from Butschli (1876), quoted in Wilson (1925).

Understanding how cell division is controlled is important for studies of growth, development and cancer in all living organisms. In recent years there has been considerable progress in our knowledge of how cell division is controlled, and it is these advances that will be dealt with in this lecture.

2. CELL CYCLE EVENTS

In most eukaryotic organisms there are similarities in the structural changes which occur at cell division (for a full description see Alberts *et al.* (1989)). Initially the nuclear membrane breaks down, often accompanied by fragmentation of other membranous structures, for example, the golgi apparatus. The chromosomes become highly condensed and as a consequence are readily visualized in the light microscope. They line up in the centre of the cell at metaphase and segregate into the newly forming daughter cells at telophase. The movements of the chromosomes require the formation of a microtubular spindle which is generated by a

Phil. Trans. R. Soc. Lond. B (1991) **332**, 271–276
Printed in Great Britain

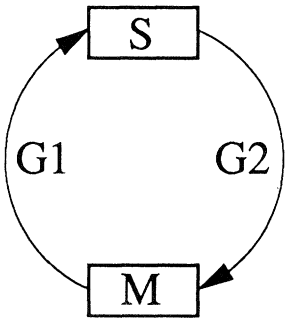

Figure 1. Major events of the cell cycle. Chromosomal replication occurs during S-phase (S), and chromosomal segregation during M-phase (M). These events are separated by two gaps, G1 between M and S, and G2 between S and M.

major reorganization of the cytoskeleton. In the vegetative cell cycle these events are known as mitosis, and are followed by cytokinesis which divides the cell into two. A modification of this process occurs during gamete formation called meiosis. This results in two successive nuclear divisions, producing four daughter cells instead of two, and reducing the chromosome complement from a diploid to a haploid level. Mitosis and meiosis are known collectively as M-phase. The events which take place during M-phase can vary from organism to organism, particularly in the simpler unicellular eukaryotes. For example, in the yeasts the nuclear membrane does not break down and the chromosomes do not always condense. However, despite these variations, the events of M-phase are highly conserved in the majority of eukaryotic organisms.

The structural changes occurring during mitosis and cytokinesis were obvious to the early microscopists (see Wilson 1925), but the remainder of the cell cycle appeared uneventful. It was only in the early 1950s that it became clear that another event, S-phase, also occurred in all cell cycles (Howard & Pelc 1953). The DNA making up the chromosomes becomes replicated during S-phase in preparation for the subsequent segregation of the replicated chromosomes during mitosis. Thus there are two major events common to all eukaryotic cell cycles, S-phase and mitosis (figure 1). Usually there are gaps between these events called G1 (for the first gap in the cycle after mitosis and before S-phase) and G2 (for the second gap after S-phase and before mitosis). These gaps can be very variable in length and in certain cell types they apparently disappear all together. An example is found in early amphibian embryos where both G1 and G2 are barely detectable (Kirschner *et al.* 1985).

3. CELL SIZE AND THE CELL CYCLE

What controls the rate of progression through the events of the cell cycle? An important clue to this problem was provided simply by looking at the size of cells. Examination of a growing microbial culture or of a tissue composed of a similar cell type reveals that cells often divide at the same size, although there are variations in different growth conditions and from tissue to tissue. A particularly clear statement of the fact that cells tend to maintain a constancy of size at division was made by D'Arcy Thompson in 1917:

> The phenomenon of division of the growing cell, however it be brought about, will be precisely what is wanted to keep fairly constant the ratio between surface and mass.
>
> D'Arcy Thompson (1917)

These and similar observations led to the idea that progression through the cell cycle was determined by the rate at which the cell accumulated mass. Implicit in this view was that specific cell-cycle events required the attainment of a critical cell mass or size before they could take place. As a consequence, the growth rate that determines the rate at which a cell accumulates mass also determines the rate of cell division. There can be exceptions to this rule although they are unusual; for example, the early amphibian embryo undergoes many cell divisions without any growth. However, this situation in the embryo cannot persist because if it were to do so then the cells would get smaller and smaller and presumably would eventually disappear!

A more mechanistic explanation of the phenomenon by which cell size influences the cell cycle was proposed in the 1960s by microbial geneticists working on DNA replication. Initiation of DNA replication occurs at a critical cell mass in *Escherichia coli*, coupling progression through the cycle with growth (Donachie 1968). This relation between cell size and the cell cycle is particularly clear in microorganisms because their rigid cell wall results in a fixed cell shape. A good eukaryotic example is the fission yeast *Schizosaccharomyces pombe*. This organism was selected for cell cycle studies because its fixed cylindrical cell shape meant that growth during the cycle could be monitored simply by measuring cell length (Mitchison 1957). Cell length at birth and division was followed in a growing culture by using time-lapse photomicrography, and established that in fission yeast, cell division required growth to a critical size (Fantes 1977). Cells that are large at birth have a shorter subsequent cycle, while those which are small at birth have a longer subsequent cycle. In both cases the cell size at the subsequent division regresses towards the average in the culture as a whole. The smaller cells need to grow for a longer period than the larger cells to acquire the critical size required for division. Cell size at division in fission yeast is also influenced by the DNA content of the cell (Nurse & Thuriaux 1980); haploid cells divide at approximately half the size of diploid cells. This relationship between ploidy and cell size has been long recognized in many organisms (see review in Nurse (1985)). For example, experiments using embryos of different ploidies showed that the greater the ploidy, the greater cell size, leading to the conclusion of a constancy between nuclear and cytoplasmic volumes called the 'karyoplasmic ratio' (Wilson 1925).

From these studies it can be concluded that a major factor determining the rate of division in many cells is the rate at which the cells accumulate mass. On attainment of a critical mass, the level of which is influenced by cell ploidy, the cell undergoes division. Size cannot be important in certain situations such as

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

the early embryo where there is no net growth and cleavage simply divides up pre-existing mass. In these circumstances the period between divisions appears to be determined by elapse of time (Kirschner *et al.* 1985), the duration of which could be set by a timer or by an oscillator.

4. INTERNAL DEPENDENCIES

A further element important in cell-cycle control concerns the dependencies operating between the major events of S-phase and mitosis. If S-phase is blocked then the subsequent mitosis is blocked also, ensuring that chromosome segregation is not initiated unless chromosome replication is complete. This dependency of mitosis upon S-phase is an example of a feedback control regulating progression through the cell cycle so that events do not take place unless all previous essential events have been completed (Weinert & Hartwell 1988). A second dependency couples initiation of S-phase to completion of the previous mitosis. Blocking mitosis prevents onset of the subsequent S-phase maintaining constancy in ploidy. These internal dependencies underlie the basic cyclic nature of the cell cycle and like the monitoring of mass and time must interact with the controls regulating onset of S-phase and mitosis.

5. CELL CYCLE MUTANTS IN FISSION YEAST

Such a complex problem as regulation of the cell cycle is best approached using genetics which allows mutants to be isolated that are altered in the controls. These mutants define the relevant genes which can then be cloned by complementing the defective function using a gene bank transformed into the mutant strain. The fission yeast is suitable for such an approach because it is convenient for both classical genetics allowing the ready isolation of mutants, and also for molecular genetics allowing cloning of the genes and their subsequent biochemical analysis.

Two types of mutant have been isolated in fission yeast. The first type were called cdc (*c*ell *d*ivision *c*ycle) mutants because they were unable to complete some event in the cell cycle leading to a block in cell division (Nurse *et al.* 1976; Nasmyth & Nurse 1981). Growth of cell mass is not impaired, and as a consequence these mutants become much enlarged. Around 30 cell-cycle genes have been identified by such cdc mutants, together with a further similar 20 genes which are required for the process of mitosis (Yanagida 1989). These 50 genes define functions required for the successful completion of the cell cycle. The second type of mutant was called wee, the Scottish word for small. Unlike the cdc mutants these can complete the cell cycle but undergo division at a reduced size (Nurse 1975; Nurse & Thuriaux 1980). These mutants are altered in the control which couples progression through the cell cycle with accumulation in cell mass. They define functions which act as major rate-limiting steps for completion of the cell cycle. A total of four genes have been identified which can be mutated in this way (Russell & Nurse 1987*a*).

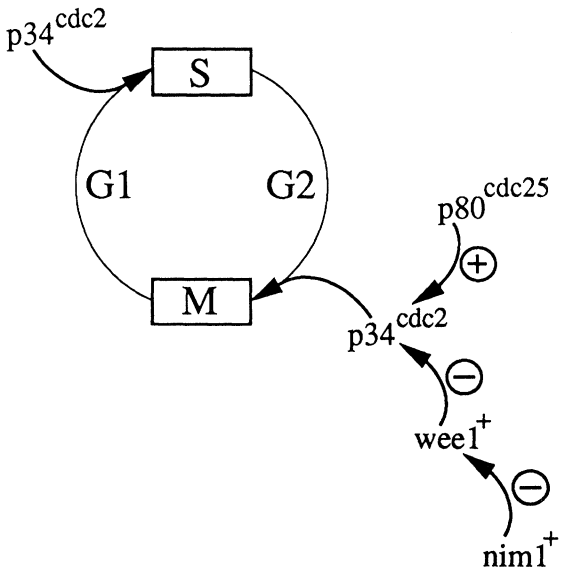

Figure 2. Onset of M is controlled by a regulatory gene network. The $p34^{cdc2}$ protein kinase is inhibited by a pathway comprising of wee1 and nim1, and is activated by $p80^{cdc25}$. The dependency of M upon the completion of S is communicated via $p80^{cdc25}$ through to $p34^{cdc2}$.

Investigation of these four genes has shown that they interact with each other in a regulatory network which determines the length of G2 and the cell cycle timing of mitotic onset. The structure of this network is shown in figure 2. It is made up of two pathways, an activatory one consisting of *cdc25*, and an inhibitory one consisting of *wee1* and *nim1* (Russell & Nurse 1986, 1987*a*, *b*). The two pathways converge on the fourth gene *cdc2*. Activation of the *cdc2* gene product brings about mitosis. All four genes have been cloned and sequenced, and the three genes *cdc2*, *wee2* and *nim1* encode putative protein kinases, suggesting that protein phosphorylation plays a key role in the mitotic regulatory network controlling mitotic onset.

6. MITOTIC REGULATORY NETWORK

The key gene in the regulatory network is *cdc2* which brings about mitosis. Antibodies have been raised using as antigens the *cdc2* protein expressed in bacteria and peptides corresponding to the predicted amino acid sequence of the *cdc2* gene (Simanis & Nurse 1986). These antibodies detect a 34 kD phosphoprotein in yeast cells, consistent with the predicted sequence of 297 amino acids. Immunoprecipitates of this protein from extracts of proliferating cells have *in vitro* protein kinase activity. A particularly good substrate of $p34^{cdc2}$ for *in vitro* protein kinase assays is H1 Histone (Moreno *et al.* 1989). This was first proposed when it was found that a purified H1 Histone kinase from starfish, cross-reacted with the yeast $p34^{cdc2}$ antibodies (Labbe *et al.* 1988). In both starfish (Labbe *et al.* 1988) and yeast (Moreno *et al.* 1989), H1 Histone kinase activity was periodic in level peaking at M-phase (see figure 3). From these and similar results with mammalian cells (Draetta & Beach 1988) it was suggested that activation of the $p34^{cdc2}$ kinase brought about mitosis

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

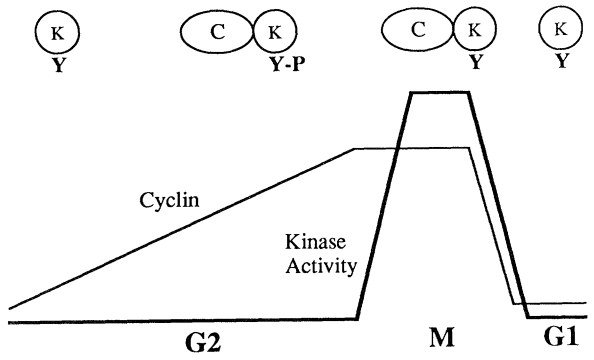

Figure 3. Scheme showing pattern of $p34^{cdc2}$ protein kinase activity during the cell cycle peaking at M. Cyclin (C) level increases during G2 and forms a complex with $p34^{cdc2}$ (K). Upon tyrosine (Y) dephosphorylation the kinase becomes active and brings about M. At the end of M cyclin becomes degraded and kinase activity falls leading to entry into G1.

by phosphorylation of certain key substrates required for mitotic onset (see later).

The cell cycle timing of $p34^{cdc2}$ kinase activation is determined by the regulatory network shown in figure 2. When a $cdc25^{ts}$ mutant is incubated at its restrictive temperature, cells arrest in late G2 with low $p34^{cdc2}$ kinase activity. On shift back to the permissive temperature, within minutes there is an increase in $p34^{cdc2}$ kinase activity followed by the initiation of mitosis (Moreno *et al.* 1989). Kinase activity remains high during mitosis and reduces to a low level as cells enter interphase. The changes in $p34^{cdc2}$ kinase activity during the cell cycle are schematized in figure 3.

The molecular basis of this activation involves phosphorylation. As cells enter mitosis $p34^{cdc2}$ becomes partially dephosphorylated (Gould & Nurse 1989). The dephosphorylation occurs mainly on a tyrosine residue (figure 3). This was mapped by conventional biochemical procedures to tyrosine 15 (Y15) in the protein. The site was confirmed by mutating it to a phenylalanine and showing that in yeast cells that contain this mutant form of *cdc2*, phosphotyrosine is no longer detected in $p34^{cdc2}$. When these mutant yeast cells were examined they were found to exhibit a pronounced wee phenotype, entering mitosis at a much reduced size. These experiments establish that altered $p34^{cdc2}$, which cannot be phosphorylated on Y15 is not inhibited and as a consequence cells enter mitosis prematurely.

The residue Y15 is located in the middle of the ATP binding site of the kinase. This suggests a simple model for the regulation of mitotic onset. During G2, $p34^{cdc2}$ is phosphorylated on Y15, which prevents the correct utilization of ATP by the enzyme and maintains kinase activity at a low level. As a consequence of *cdc25* activity, Y15 becomes dephosphorylated (figure 3) and ATP can be correctly utilized, leading to an increase in kinase activity and mitotic onset.

7. DEPENDENCY UPON S-PHASE

The regulatory pathway consisting of *cdc25* activating *cdc2* is also responsible for establishing the dependency of mitosis upon S-phase. Mutants in *cdc2* which produce an altered form of $p34^{cdc2}$ that does not require *cdc25* for activation, are defective in this dependency. When S-phase was blocked in one such mutant (called *cdc2*-3w), mitosis was still initiated resulting in a lethal attempt by the cell to segregate its chromosomes even though they were not replicated (Enoch & Nurse 1990). The terminal phenotype of these cells was cut-like (Hirano *et al.* 1986), with the septum of the dividing cell cutting the nucleus in two. A similar phenotype was also seen with the F15 mutant of *cdc2* that does not require *cdc25*, and with cells that contain an elevated amount of $p80^{cdc25}$ (Moreno *et al.* 1990; Enoch & Nurse 1990). In contrast, blocking S-phase in mutants altered in the *wee1* regulatory pathway also blocked onset of the subsequent mitosis showing that the dependency is maintained in these mutants.

These experiments establish that the cell-cycle dependency coupling mitosis to completion of S-phase operates through $p34^{cdc2}$ and $p80^{cdc25}$. Presumably when S-phase is normally completed a signal can be sent to $p34^{cdc2}$ via $p80^{cdc25}$, which allows initiation of mitosis. If S-phase is not completed then the signal is not sent, preventing Y15 dephosphorylation and blocking onset of the subsequent mitosis. In this way cells ensure that mitosis and division only take place when chromosomal replication is properly complete.

8. CONTROL IN OTHER EUKARYOTES

Two lines of evidence have established that these controls are also operative in eukaryotes more complex than fission yeast. The first experiment was the cloning of the human homologue of *cdc2*. The usual way to clone homologues from different organisms is to look for genes of similar structure. Various strategies can be used to detect similarities in DNA sequence such as reduced stringency hybridization in Southern blots or the polymerase chain reaction (PCR). Alternatively, similarities in protein structure can be detected by using antibodies and a bacterial expression library. However the human *cdc2* homologue was cloned in a different way based on function (Lee & Nurse 1987). A human cDNA library which could be expressed in fission yeast was transformed into a $cdc2^{ts}$ mutant, and clones isolated that could grow at the restrictive temperature. These clones contained a human cDNA encoding a gene with 63% identity in amino acid sequence to fission yeast *cdc2*. In addition, this human gene was functionally equivalent to the yeast gene, strongly arguing that very similar cell cycle controls are also operative in human cells.

The second line of evidence involved the purification of maturation promoting factor (MPF) from Xenopus eggs. MPF induces G2 arrested oocytes to undergo meiotic M-Phase resulting in maturation of the oocytes into eggs. Originally, MPF was transferred into oocytes by injecting extracts from eggs. The purification of MPF from these complex extracts proved difficult, but was finally achieved by Lohka *et al.* (1988). The purified MPF contained two proteins, one being of 32kD which cross-reacted with the yeast *cdc2* antibodies

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

(Gautier *et al.* 1988). The second protein turned out to be a cyclin, an important cell cycle regulator first identified in marine invertebrate embryos but also found in many eukaryotes including fission yeast, Xenopus, and mammalian cells (Hunt 1989). Cyclin is associated with $p34^{cdc2}$ in all of these organisms. It oscillates in level during the cell cycle peaking at M-phase, and needs to accumulate to a critical amount in order to allow activation of the $p34^{cdc2}$ kinase (see scheme shown in figure 3).

These results establish that $p34^{cdc2}$ and other elements of cell cycle control are conserved in all eukaryotes. Furthermore, functional equivalence of $p34^{cdc2}$ in humans and yeast and its involvement in M-phase control in Xenopus and yeast indicates that its regulation and mode of action are also likely to be highly conserved. This even applies to the precise biochemical mechanism of $p34^{cdc2}$ kinase activation, which in vertebrate cells also involves dephosphorylation of Y15 (Chris Norbury, unpublished results).

9. UNIVERSAL MITOTIC CONTROL

This conservation suggests that there is a universal mitotic control common to all eukaryotic cells (Nurse 1990). At the centre of this control is the $p34^{cdc2}$ kinase associated with cyclin and activated by $p80^{cdc25}$. Homologues to *cdc25* have now been found in Drosophila (Edgar & O'Farrell 1989; Jiminez *et al.* 1990) and humans (Sadhu *et al.* 1990), indicating that this aspect of the control is probably also conserved. On completion of S-phase $p80^{cdc25}$ becomes potentially active and can bring about $p34^{cdc2}$ kinase activation at the end of G2.

The active kinase probably initiates mitosis by phosphorylating key substrates which bring about the major events of mitosis. These are not yet completely identified but here already a number of good candidates (Moreno & Nurse 1990). For example, H1 histone phosphorylation (Langan *et al.* 1989) may contribute to chromosome condensation (Bradbury *et al.* 1974), lamin phosphorylation to nuclear envelope breakdown (Peters *et al.* 1990), centrosomal protein phosphorylation to spindle generation (Bailly *et al.* 1989), and $p60^{src}$ phosphorylation to cell-shape changes (Shenoy *et al.* 1989; Morgan *et al.* 1989).

What is less clear is how the regulatory network interacts with the monitoring of cell mass in growing cells and with the elapse of time in non-growing cells such as embryos. These important questions remain for the future. I would like to end on a sobering note. The conclusion drawn here, that there is a universal mitotic control, was first proposed by one of the proponents of the cell theory, Schwann, as early as 1839:

> We have seen that all organisms are composed of essentially like parts, namely of cells; that these cells are formed and grow in accordance with essentially the same laws; hence, that these processes must everywhere result from the operation of the same forces.
>
> Translation from Schwann in Untersuchungen (1839) quoted in Wilson (1925)

It has taken us nearly 150 years to establish that this early speculation was correct!

REFERENCES

Alberts, B., Bray, D., Lewis, J., Raff, M., Roberts, K. & Watson, J. 1989 *Molecular biology of the cell* (2nd. edn) New York and London: Garland Publishing.

Bailly, E., Doree, M., Nurse, P. & Bornens, M. 1989 $p34^{cdc2}$ is located in both nucleus and cytoplasm; part is controsomally associated at G2/M and enters vesicles at anaphase. *EMBO J.* **8**, 3985–3995.

Bradbury, E. M., Inglis, R. J., Matthews, H. R. & Langan, T. A. 1974 Molecular basis of control of mitotic cell division in eukaryotes. *Nature, Lond.* **249**, 553–556.

Donachie, W. D. 1968 Relationship between Cell Size and the Time of Initiation of DNA Replication. *Nature, Lond.* **219**, 1077–1079.

Draetta, G. & Beach, D. 1988 Activation of cdc2 protein kinase during mitosis in human cells: cell cycle-dependent phosphorylation and subunit rearrangement. *Cell* **54**, 17–26.

Edgar, B. & O'Farrell, P. 1989 Genetic control of cell division patterns in the Drosophilla embryo. *Cell* **57**, 177–187.

Enoch, T. & Nurse, P. 1990 Mutation of fission yeast cell cycle control genes abolishes dependence of mitosis on DNA replication. *Cell* **60**, 665–673.

Fantes, P. 1977 Control of Cell Size and Cycle Time in *Schizosaccharomyces pombe*. *J. Cell Sci.* **24**, 51–67.

Gautier, J., Norbury, C., Lohka, M., Nurse, P. & Maller, J. 1988 Purified maturation-promoting factor contains the product of a Xenopus homolog of the fission yeast cell cycle control gene cdc^{+}. *Cell* **54**, 433–439.

Gould, K. L. & Nurse, P. 1989 Tyrosine phosphorylation of the fission yeast $cdc2^{+}$ protein kinase regulates entry into mitosis. *Nature, Lond.* **342**, 39–45.

Hirano, T., Funahashi, S., Uemura, T. & Yanagida, M. 1986 Isolation and characterization of *Schizosaccharomyces pombe* cut mutants that block nuclear division but not cytokinesis. *EMBO J.* **5**, 2973–2979.

Howard, A. & Pelc, S. R. 1953 Synthesis of desoxyribonucleic acid in normal and irradiated cells and its relation to chromosome breakage. *Heredity, Lond.* **6**, 261–273.

Hunt, T. 1989 Maturation promoting factor, cyclin and the control of M-phase. *Curr. Opin. cell Biol.* **1**, 268–274.

Jiminez, J., Alphey, L., Nurse, P. & Glover, D. 1990 Complementation of fission yeast $cdc2^{ts}$ and $cdc25^{ts}$ mutants identifies two cell cycle genes from Drosophila: a cdc2 homologue and string. *EMBO J.* **9**, 3565–3571.

Kirschner, M., Newport, J. & Gerhart, J. 1985 The timing of early developmental events in Xenopus. *TIG* **1**, 41–47.

Labbe, J. C., Lee, M. G., Nurse, P., Picard, A. & Doree, M. 1988 Activation at M-phase of a protein kinase encoded by a starfish homologue of the cell cycle control gene $cdc2^{+}$. *Nature, Lond.* **335**, 251–254.

Langan, T. A., Gautier, J., Lohka, M., Hollingsworth, R., Moreno, S., Nurse, P., Maller, J. & Sclafani, R. A. 1989 Mammalian growth-associated H1 histone kinase: a homolog of $cdc2^{+}$/CDC28 protein kinases controlling mitotic entry in yeast and frog cells. *Molec. cell Biol.* **9**, 3860–3868.

Lee, M. G. & Nurse, P. 1987 Complementation used to clone a human homologue of the fission yeast cell cycle control gene cdc2. *Nature, Lond.* **327**, 31–35.

Lohka, M. J., Hayes, M. K. & Maller, J. L. 1988 Purification of maturation-promoting factor, an intracellular regulator of early mitotic events. *Proc. natn. Acad. Sci. U.S.A.* **85**, 3009–3013.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Mitchison, J. 1971 *The biology of the cell cycle*. Cambridge University Press.

Mitchison, J. 1957 The Growth of Single Cells. 1. *Schizosaccharomyces pombe*. *Expl Cell Res.* **13**, 244–262.

Moreno, S., Hayles, J. & Nurse, P. 1989 Regulation of $p34^{cdc2}$ protein kinase during mitosis. *Cell* **58**, 361–372.

Moreno, S., Nurse, P. & Russell, P. 1990 Regulation of mitosis by cyclic accumulation of $p80^{cdc25+}$ mitotic inducer in fission yeast. *Nature, Lond.* **344**, 549–552.

Moreno, S. & Nurse, P. 1990 Substrates for $p34^{cdc2}$: In vitro veritas? *Cell* **61**, 549–551.

Morgan, D. O., Kaplan, J. M., Bishop, J. M. & Varmus, H. E. 1989 Mitosis-specific phosphorylation of $p60^{c\text{-}src}$ by $p34^{cdc2}$-associated protein kinase. *Cell* **57**, 775–786.

Nasmyth, K. & Nurse, P. 1981 Cell division cycle mutants altered in DNA replication and mitosis in the fission yeast *Schizosaccharomyces pombe*. *Molec. gen. Genet.* **182**, 119–124.

Nurse, P. 1975 Genetic control of cell size at cell division in yeast. *Nature, Lond.* **256**, 547–551.

Nurse, P. 1985 The Genetic Control of Cell Volume. In *DNA and evolution: natural selection and genome size* (ed. T. Cavalier-Smith), pp. 185–196. London: John Wiley & Sons.

Nurse, P. 1990 Universal control mechanism regulating onset of M-phase. *Nature, Lond.* **344**, 503–508.

Nurse, P., Thuriaux, P. & Nasmyth, K. 1976 Genetic control of the cell division cycle in the fission yeast *Schizosaccharomyces pombe*. *Molec. gen. Genet.* **146**, 167–178.

Nurse, P. & Thuriaux, P. 1980 Regulatory genes controlling mitosis in the fission yeast *Schizosaccharomyces pombe*. *Genetics* **96**, 627–637.

Peter, M., Nakagawa, J., Doree, M., Labbe, J. & Nigg, E. 1990 In Vitro Disassembly of the Nuclear Lamina and M Phase-Specific Phosphorylation of Lamins by cdc2 Kinase. *Cell* **61**, 591–602.

Russell, P. & Nurse, P. 1986 $cdc25^{+}$ functions as an inducer in the mitotic control of fission yeast. *Cell* **45**, 145–153.

Russell, P. & Nurse, P. 1987 The mitotic inducer $nim1^{+}$ functions in a regulatory network of protein kinase homologs controlling the initiation of mitosis. *Cell* **49**, 569–576.

Russell, P. & Nurse, P. 1987 Negative regulation of mitosis by $wee1^{+}$ a gene encoding a protein kinase homolog. *Cell* **49**, 559–567.

Sadhu, K., Reed, S., Richardson, H. & Russell, P. 1990 Human homolog of fission yeast cdc25 mitotic inducer is predominantly expressed in G2. *Proc. natn. Acad. Sci. U.S.A.* **87**, 5139–5143.

Shenoy, S., Choi, J. K., Bagrodia, S., Copeland, T. D., Maller, J. L. & Shalloway, D. 1989 Purified maturation promoting factor phosphorylates $pp60^{c\text{-}src}$ at the sites phosphorylated during fibroblast mitosis. *Cell* **57**, 763–774.

Simanis, V. & Nurse, P. 1986 The cell cycle control gene $cdc2^{+}$ of fission yeast encodes a protein kinase potentially regulated by phosphorylation. *Cell* **45**, 261–268.

Thompson, D. 1917 *On growth and form* (1st edn). Cambridge University Press.

Weinert, T. & Hartwell, L. 1988 The RAD9 gene controls the cell cycle response to DNA damage in *Saccharomyces cerevisiae*. *Science, Wash.* **241**, 317–322.

Wilson, E. B. 1925 *The cell in development and heredity* (3rd. edn). New York: Macmillan Co.

Yanagida, M. 1989 Gene products required for chromosome separation. *J. Cell Sci.* **12**, 213–229.

Lecture delivered 26 February 1990 at the John Curtin School of Medical Research, Australian National University; typescript received 16 January 1991

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES