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MORPHOGENESIS _A VIEWPOINT; OR How does the tulip know it is spring.

Cell differentiation viz a viz morphogenesis has beenone of the most challenging problems of cell biology.Our presentknowledge of morphogenesis the growth of organism into the fullness of morphological and functional entity that it is, from the blueprints of a c tio n and growth ; uniquely coded into the genetic complement of a single parent cell-the zygote ;is not yet capable answering a simple child's query that is the alternate title . The best o ne could imagine isthat, all the genetic information is passed on to the primordial zygote like it were a written play and with all the charecters back drops and even the cues predefined . The complexity of the play make the cue sitters very relevant nay crucial though at intermediate acts the experienced players may well carry on for awhile without the cues.

The very morphology recreated insuch precision over and over again tells one immediatly that in members of a species each cell of the organism has to find its unique placement in the organismic lattice and quite similarly in members of a species.This becomes evident by looking at fig]. The pattern]a can bereproduced only if cell] sits on top of cell2 which in turn sits on top of3 This is trivial example but hopefully illustrates the point.The problem is made a little more complex since morphologically,there defenitely is a lot of freedom in design, even amongst cells in a semiclone.Thus t h e p problem of morphogenesis canbe at best rationalised into one of finding a way of specifying cells uniquely in as simple a manneras possible;then proceeding to explain in terms of such uniqueness how one could specify the fundamental charecteristics of the cell

There is not a single question in biology which can be posed i n isolation with respect to the other fundamental questionsI.Many times it has perhaps been more rewarding to keep in view the many oher questions classical biology has asked .Any general formulation will have to take into account these questions like vegetative reproduction,transdetermination,polyploidy,polyembryonism,etcto name a few.

These are no way new thoghts,though biological fashion has a tendency to ignore old masters; it is worth recalling a few.]900-Driesch,'fate of an embryonic cellis afunction of its position in the organism.'.Even in]878 H .Vochtung said thatt the way in which a cell differentiates is determined by its position in the plant. Even Nehemia Grew(]678-]682)percieved that in"The beautifull architectural geometry of differentiated tissue all of these structures or conformations have been contrived and brought about in am mechanical way". D'Arcy Thomson(]9]7)said that in every organic development involving metabolism growth and morphogenesis for which biologists have advanced interpretatins of a biological kind there must also be some understanding of the inseparable physical factors and mathematical relationships ,for these are quite basic to allthe phenomena where sceince is concerned. Wardlaw(]965) said "that acell may differentiate as it does because it is part of a holistic pattern derived from the working of unitary reaction system

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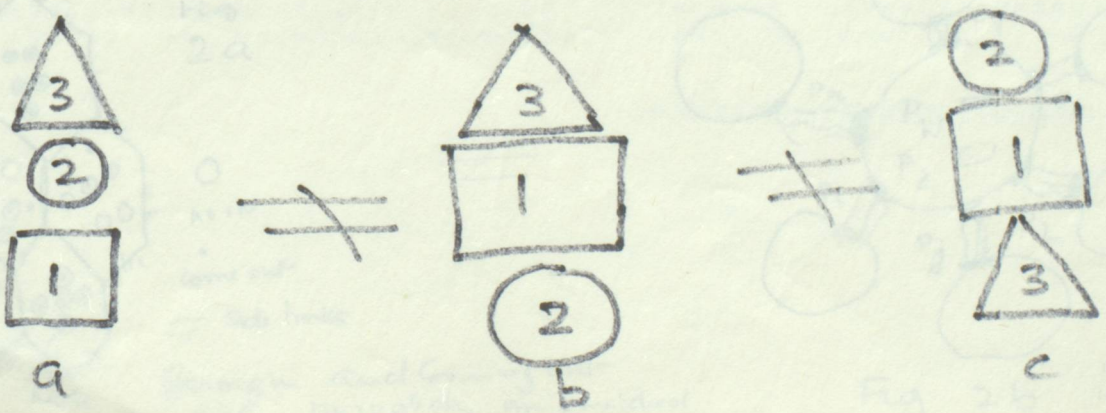
Of recent times the approaches have tended to be three fold;
]. The essentially pragmatic epigenetic approach;
physdologists' approach in terms of general plant ot cell physiology incudes:
a.Factors referable to stage reached in ontogeny
b.Endogenous factors involved in cohesion and other organismal relationships.
cGeneral and specific metabolites,sugars,aminoacids,cytokinins,etc limitting or specifically active during morphogenesis.
d.Environmental ; light,heat,etc.
2Morphogenetic approach:morphological and anatomical work being the basis as substrates in the organismal reaction system undergo changes specific enzymes ievoked etc
3The molecular biology approach: devolopment referred to as evocation and acti on of genes on a specified genome programme coded in chromosomes (almost a preformation sort of view one must say)

Obviously this cannot be understood in terms of genome difference,since the chromosomal contents of the differentiated cells have been verified to be chemically equi vaent.Also it has been possible to either accelerate or decelerate morphogenetic movements by apprpriate inducer substances usually enzymesThe genome reminded Wardlaw one of the merits of democracy' "Some genes arw active all the time allthe genes some time not all the genes all the time".A school of thought led by Crick ,Rosen,and Waddington believes cell differentiation to be a macroprocess being guided by concentration gradients of presumptive morphogens.One has to assume then that it is chance that decides what role a particular cell plays in the organism.Again the experimental findings of Sperry and Weiss on chemospecificity of nerve cells would have to be seen as a quantitative than qualitative one.;atleast in the first order Reliability of a system doubtless improves when based on qualitative rather than quantitatiesA. Assuming cells need to have distinct tags proteins because of their versatility stand out as likely candidates for such a unique specification.This is particularly pleasing in terms of economy of types and also since genes can directly code only for proteins.

This made Wasserman come up with the idea of differentiated cells synthesising"cell unique proteins"or rather because they synthesise cell unique]2proteins they are differentiated.However since there may [2 be about]0 different cells in a fullgrown organism,this demandedi]0 genes in the chromosomal DNA for synthesising these proteins.Obviously the genetic material in a single cell cannot hold such an amount of directly coded message. This led to information theorists to suggest that a cell can never contain all the information required to grow into af full organism. Wasserman tries to overcome this difficulty by]working out a combinatorial procedure to arrive at approximately 5x]0 protein type s using only a few number of genes-]88.To argue his case hehas his innumerable hypotheses mechanisms and programmes.and more than that he refutes the fairly established basis of molecular biology the one cystron one polypeptide theory

FIG 1



AN OVERVIEW OF THE PRESENT FORMULATION:

Starting with the basic facts that differentiated cells are chemospecific and proteins can very well influence the synthesis and function of new ornew combinations of proteins an attempt is made to look at the following;

a.How does the zygote grow giving rise to an astronomical number of differentiated cells of a full grown organism?

b.How does each cell recognise its position(address) in the organism? (Morphogenetic movement?)

c.How does the zygote give rise to unfailingly organisms with a remarkable degree of similarity (in the same species)?

The following premises are made in an attempt to elucidate these;

].Postulated existence of a handfull of(say n ; n may be 5 or 6 or]0 "TECTORIAL PROTEINS";surface proteins inter linking cells;-these are species specific.(It will be shown later that these need not necessarily interlink cells.Their existence on the surface is a must)

2.Every chromosome in the cell contains the blue prints of these, THis again is modifiable, it is possible that thse present in many if nott all.

3·For simplicity one assumes each cell to have eight neighbours in a hexagonal close packing six around one above one below .This means each cell has at least eight regions in its outer membranes populated by these "TECTORIAL PROTEINS" which in turn are linked (Associated) to such "TECTORIAL PROTEINS" og the neighbouring cells.

4· The pre sence of these proteins on such regions,probably desmosomes may be surface antigens or even membrane proteins (these have to be common to all tissue and all organisms of a species);with their associated ions and conformational variabilities give rise to physical potential characteristic of this region This in turn invests the cell with a free energy of its own.

5.The "TECTORIAL PROTEINS" of one cell surface are linked to those of the neighbouring cell by local interactions viz ionic hydrophobic hydrogen bond formation etc.This is not a nessessary premise but most probably is a stabilising influence on cell association.

6.Considering o ne such interface ,assuming that there are mdifferent tectorial proteins(these m may be a combinatorial subset of the say n species specific tectors);there are m! waysof linkingthese with those of the neighbouring cell.Since each cell can have eight neighbouring cellsit can exist in m^8 different neighbourhood associati-

$$C_8$$

ons thro' threse tectors; this essentially endows each cell with a unique character. For instance considering the simplest case of m=5 we can have 5!

$$C_8 =]20 \times {}_5C_8 = \text{about } 3000,000,000,000 \text{ unique cell types .}$$

In essence ,somatic cells need not synthesise cell unique proteins,or(as suggested by Wasserman0) to be in the differentiated state but must possess the cell unique combination of tectors(this in turn will be shown to an accident of its history)

Fig 2 illustrates the principle ;here it is assumed that m=5 and the linking of a particular order of these protiens of one cell surface with those of a neighbouring cell(in perhaps the same or different order) is called a permmutation.Fig 3.(It is to be noted that the link is an abstraction ,the very disposition and consequent differences in association is suufficient,note fig 2a.)

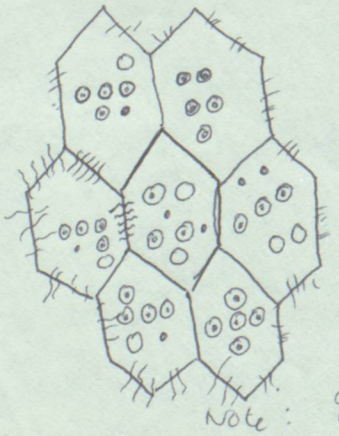
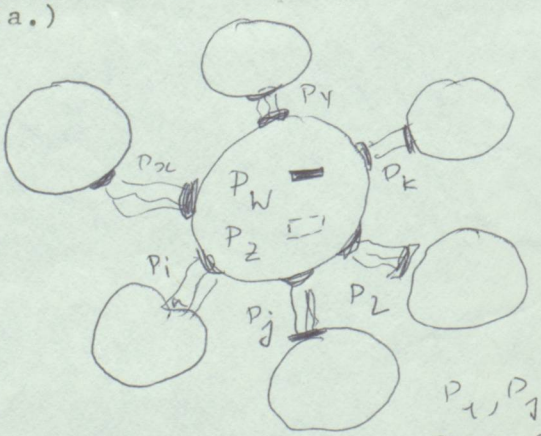


Fig 2a

Note: Goingin and Coming out are purposely omismatched.



$P_1, P_j \ldots P_3$ may not be identical.

Fig 2b

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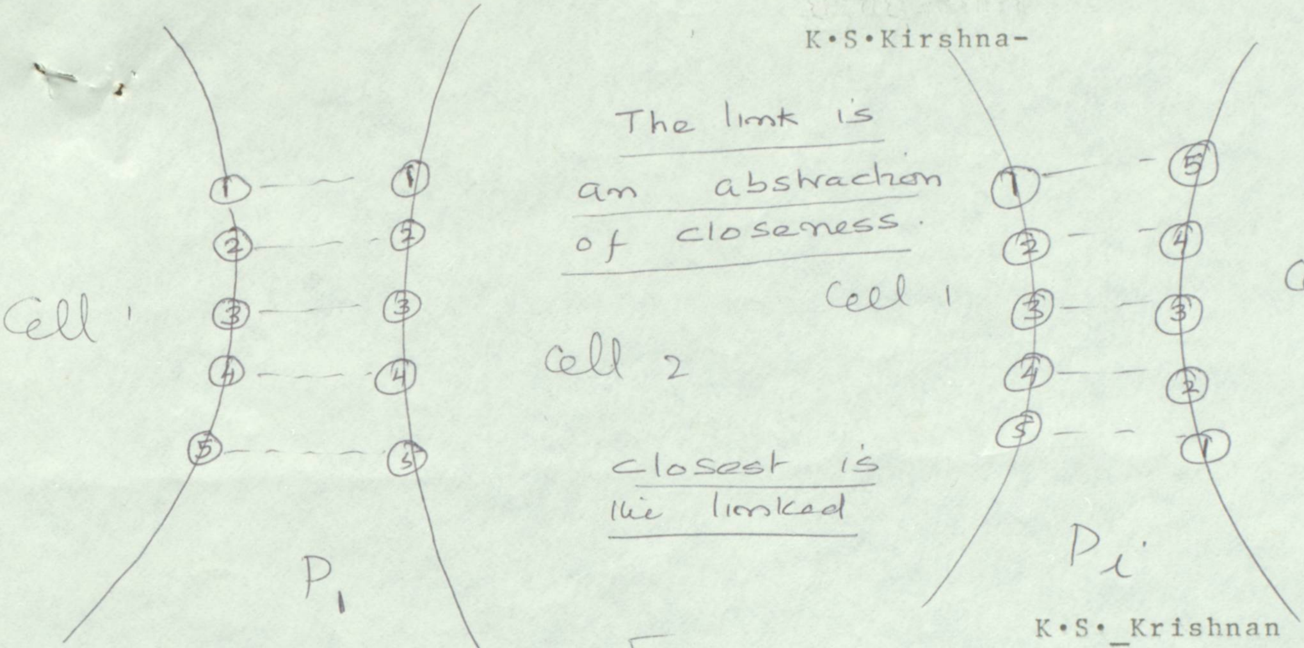

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Fig 3.

Hence at the completely differentiatedstage, each clone in its combinatorial linking of these tectors with their neighbours as depicted in fig]a& fig]b

7. Now let us look at the process of growth from thre zygote. When the zygote devides ,even as the new cell membrane interface is synthesised ,the tectorial protiens come into play. As the number of cells increase ,the local potential changes caused by the different permutations of tectorial protiens reach a certain perturbing state where the cells are forced to move about (in search of new partners)to regions of local minimum free energy , there by ensuring a global minmimum free energy of thr entire system. This is morphogenetic movement. Thus moving about the tectorial proteins at the different sides are going to find themselves in a myriad of different environments for finite intervels of time and each of them undergoes different conformational changes and this could cause the cell to be endowed with a heirarchy of enzyme induction spatially and or temporally This might ensure (by acooperative effort onthe part of chromosomes) what combinations of the species specific tectors should be synthesised in the future to decide the characteristics of this cell and its progeny.

Before proceeding further we have to answer the following;

].Why do we require different combinations of the species specific tectorials to synthesised by any cell?

2.What do we mean by cooperative effort on the part of chromosomes?

(both these are explained on the basis of simplistic arguments,the abstract hypothesis is not based on these assumptions or answers since the cell uniqueness is teleologically plausible even if the tectors are ordinary membrane molecules.0)

IN principle it is agreed that the ~~differentxxcellsxxarex~~ differentiated cells areunique in theur chemical specificity,. In this view this uniqueness is achieved by the different combinatorial environments asdepicted in fig] .The difference between somatic cells on the basis of chemical specificity can be one in kind or degree

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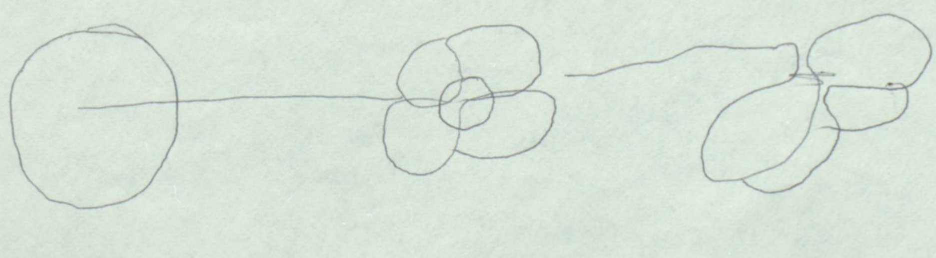

The somatic cells of the samekind may yet differ in gradation or degree of t their c hemical specificity. To cite am example the brain or the liver cells are of different kinds while the difference betweenthe cells in the liver might be one of degree.
The cells of the different kind are hypothesised to synthesise different combinations of the species specific tectorial protiens,w hile t he cells of the same kind synthesise the same set of protiens yet may be different due top the permutations of the side links possible with the neighbours
We know the at chromosomal abberations could be to lerated by morphology to a ce rtain extentd nt

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