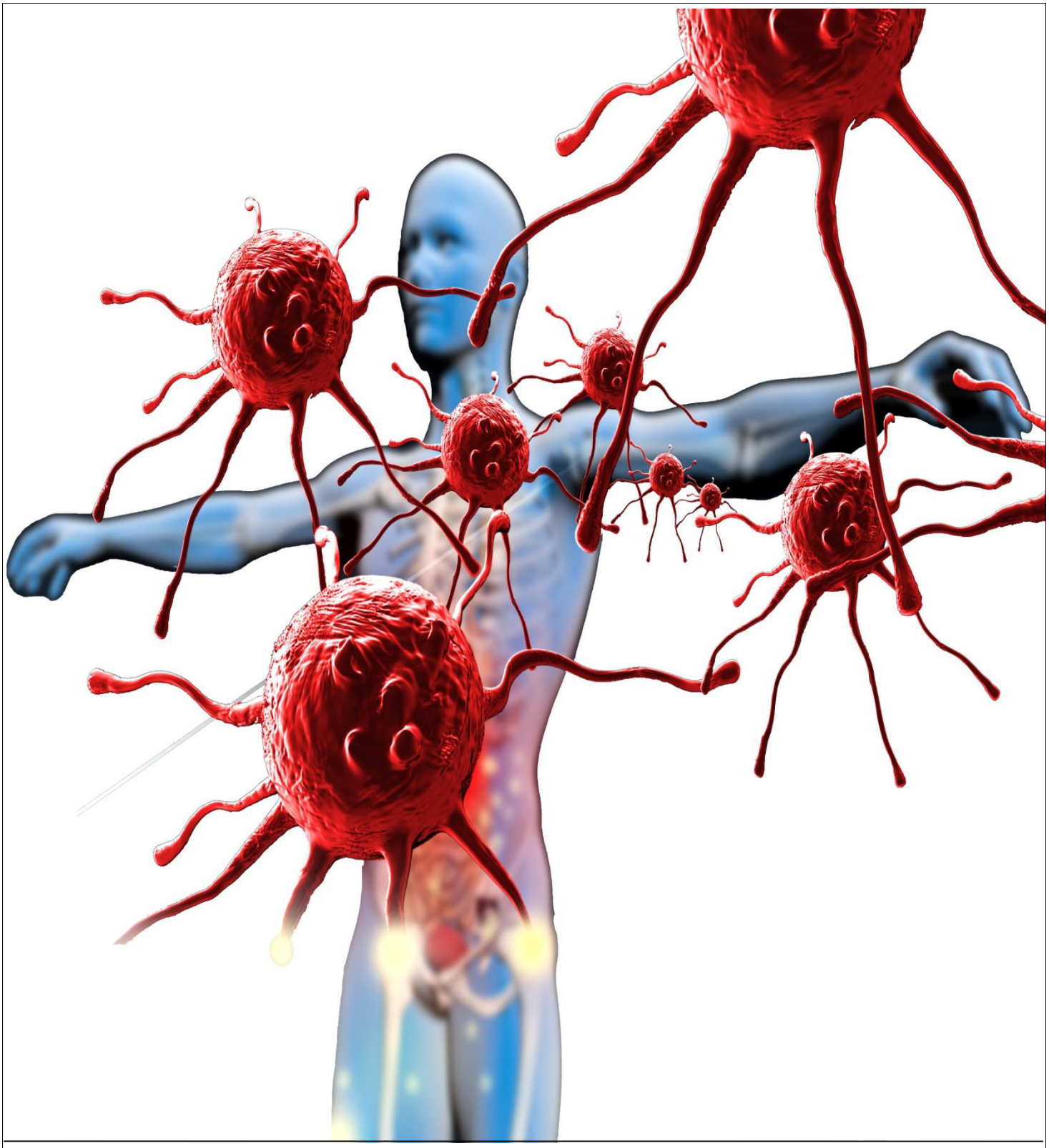

IMMUNOLOGY

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#12

By Mohammed Nawaiseh

Cytotoxic T + B cells' Activation

Cytotoxic T cell Activation

The activation of cytotoxic T cells reacquires the presentation of Ags on MHC-1; the TCR on cytotoxic T cell will sense the MHC-1-Ag complex. The Ag caught could be of an abnormal, virally infected, or cancerous cell. The presentation of the complex is mediated by APC, and this is the second signal to achieve proper activation. (The cytotoxic T cell is not able to be activated by only one signal which is from the infected cell, one signal isn't enough; it needs another signal which is provided by an APC to achieve the activation of cytotoxic T cell). The dendritic APC can phagocyte the virus and introduce some certain endogenous Ags on its surface bound to MHC-1 molecule. The TCR will recognize this complex after approximation and adhesion of the two cells. As we said, for the T cell to be activated we need 2 signals: CD8 of cytotoxic T cell associates with the alpha-3 domain of the alpha chain of MHC I, and this transmits the signal to the inside. So now we have a signal transmitted to the inside through CD8 and CD3, and also CD45 can be involved too →this is the 1st signal, now we need another 2nd signal; this comes from the ligation of B7 "on APC" with CD28 "on cytotoxic T cell".

Many factors contribute to the proliferation and expansion of activated T cell, such as: the presence of IL-2 that's predominantly secreted by CD4+ Helper T cells, noticing that CD8+ cells themselves can also produce it. IL-2 binds to its receptor on the activated cells. Some say that this is not the case and IL-2 produced by less activated CD4 cells is not enough, so they suppose that what is more likely to happen is that during the participation of CD4 cell; they imagine that the APC that is having the Ag inside it will have an endogenous part expressed as the Ag-MHC I complex & also have an exogenous part (from the environment) which works as a stimulator for CD4+ Helper T cells, so we've activation of both cells at the same time, not necessarily by the same epitope but by the same type of foreign antigen. Then once the CD4 cell is activated, it produces a lot of IL-2 which activates CD8 cells by working in a paracrine fashion.

Once the CD8+ T cell is activated, it will produce a clone. Part of the clone will be the **effector cells**, aka the **cytotoxic Armed cells** or **Primed cells**. The other part of the clone is the Memory cells. The Armed cells will attack any cell with Ag-MHC1 complex on surface.

The Armed cell will attack these complexes on the infected cells as well as the APCs. The cell will recognize that complex, and then inject its "Perforin" & "Granzymes" into the target cell to induce its apoptosis. (Granzymes activate the Caspases.)

A second mechanism by which apoptosis can be induced is the expression of FAS-Ligand on the CD8+ cell, to be linked to its receptor on the target cell FAS (death receptor).

The CD8+ cell after killing its target cell, it will leave to kill other target cells. It will stay there for weeks until the whole immune response comes to an end.

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THE END of this topic.

➔

B cells Activation

B cells can recognize the Ag by itself, without processing or presentation by APCs. To activate a B cell, you need to have a crosslinking of two immunoglobulin receptors. Two Igs on the surface of a B cell will join the specific epitope; this joining will send **the first signal** to the cell through the Ig-Alpha and Ig-Beta connected to the BCR. The signals are sent by stimulating other markers too, one of them is a tri-molecular complex which presents on the surface of B cell and it's called the "triple marker" being composed of CD19 (B cell marker), CD21 (complement receptor 2), and CD81 molecules.

A second signal to be initiated needs the activation of a Helper T cell. The activation of a Helper T cell in this case is mediated through the B cell itself. The B cell will work as an APC (macrophage); it will internalize the Ag, process it as an exogenous Ag, and introduce its pieces to the surface with MHC II molecules. These newly synthesized MHC II-Ag complexes on the surface of B cell will activate the T Helper cell through CD20. The activated CD4+ Helper cell will start secreting CD28 and CD40-Ligand that has its receptor (CD40 Receptor) on the B cell. The binding of the CD40-L to its receptor will achieve the *proper activation* of the B cell, its proliferation, the affinity maturation of Igs, and the isotype switching between IgM and other Igs. This Helper cell (Helper-2) will secrete certain cytokines [IL2, "mainly IL4", IL5, and IL6] to maintain the proliferation of the activated B cell.

[In certain diseases where the CD40-L and CD40R are absent, the cell can still be activated by the second signal of CD28, but you don't expect to have isotype switching or affinity maturation, so the CD40-L+R are really important for B cell proper activation.]

➔ You can say, as a rule:

TH1 cells → CD4+ cells which have been stimulated by macrophages

TH2 cells → are CD4+ cells which have been stimulated by B cells.

Once the B cell is activated by the two signals, it will proliferate producing a clone. The clone will contain effector "Armed" cells and Memory cells. The Memory cells go to lymph nodes and remain there for a long time; they also may express a marker on their surfaces: CD27. "As a rule (not always), if CD27 presents on B cell surface usually it's a memory B cell".

The effector B cells will become Plasma cells to be able to produce antibodies. Plasma cells usually are located in the medulla of Lymph nodes, spleen, and bone marrow. The first Ig to be secreted is the IgM type (for primary response). Some plasma cells live for a short time; they may die after producing certain Abs to fight the infection, BUT to have a long-term immunity: other plasma cells will live for a long time and keep producing Abs.

➔ Remember that the cellular-mediated immune responses remain effective for very long time, like in Measles; if you're infected, you probably will never be infected again. While Humoral-mediated Immunity (Abs) lasts only for years, like when you get the vaccine of Tetanus (Abs), you need to take a booster of the vaccine after 10 years.

- The antigen of B cell can either be free-floating or presented by APCs such as macrophages or dendritic cells (DCs), and include proteins, glycoproteins, polysaccharides, and lipid

➢ Activation of B cell:

✓ It can be activated by :

1. T dependent Ags (proteins)
2. T independent Ags (polysaccharides)

• 1)T Cell-Dependent B Cell Activation

✓ They are named as such because they are unable to induce a humoral response in organisms that lack T cells

✓ The story now continues as before since the B cell has become an **APC** with CD40 receptor interacting with CD40 ligand on {T-Helper 2} cells.

➢ Activation of T dependent B cell

✓ B cells recognize antigens in its native form.
✓ You need two adjacent BCRs engaged so that you can get initial activation or two IgMs that have been **cross-linked** by the antigen so that will give you the **first signal**.
✓ The signals are also provided by **a trimolecular complex present** on B cells.
✓ Antigen and its receptors are internalized inside the B cell and broken down in the lysosomes into peptides.
✓ These peptides are displayed on the surface of the B cell in conjunction with **MHC Class II molecule.**
✓ Ag – MHC 2 complex will activate T-helper 2 through **CD20**
✓ **Activated T-helper start secreting {CD28 and CD40 ligand }**
✓ We always need a **second signal** when activating B lymphocytes. And this is provided by the products of T-helper cell (CD28 and CD40 ligand).
✓ This CD4 T cell will produce IL-2 and IL receptor and now it will be ready to produce cytokines for B cell.
{Production of IL-4, IL-5 and IL-6 which will further promote the growth of B cell and maturation.}
✓ B cells produce antibodies, first one being IgM and then there's **isotype switching**

• 2) T-Independent Antigens

✓ Antigens that activate B cells without T cell help are known as T cell-independent and include foreign polysaccharides antigens.

✓ They are named as such because they are able to induce a humoral response in organisms that lack T cell

- How to activate a B-cell without a 2nd signal from helper T cell? We have 2 theories:
  1) Polysaccharides are made of **repeating epitopes** (units of sugars)
     - ✓ -They have repeating similar units, they can **cross-link many BCRs** and by doing so, they can **activate the cells.**
     - ✓ -Activated B cells **will not have memory** cells and will **only produce IgM** which is of **low affinity.** And there's no class switching and no affinity maturation.

     Example : group A and B in blood grouping

  2)Polyclonal activators of B Cells e.g. LPS (lipopolysaccharide)

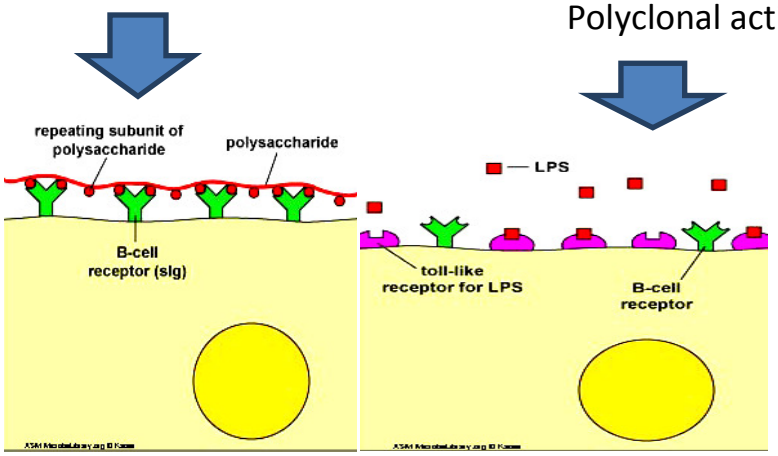
  -Also here we **don't have switching of Igs**

  -**No memory** cells are produced

  -B cells need additional signals to complete activation, but instead of receiving them from T cells, they are provided by recognition and binding of a common microbial constituent {antigen likes LPS}to toll-like receptors (TLRs) which act as second signals for activation of T-independent B cell.

Polysaccharides with repeating units of sugars

Polyclonal activators of B Cel



Memory B cell activation:

- ✓ With each such subsequent exposure to the **same antigen**, the number of different responding B cell clones increases to generate a polyclonal response and effectively a greater number of memory B cells persist. Thus, a **stronger** antibody response having improved affinity towards antigen is typically observed in the secondary immune response

- ✓ In a B cell primary response to a T-dependent antigen, the immune system selects B cells with a **high affinity and specificity** for the antigen and these become **memory cells.**

Difference between "Primary Immune Response" and "Secondary Immune Response"

✓ Primary Immune Response:

- This immune response occurs as a result of the first contact with an antigen
- It takes longer time to establish immunity.
- It declines rapidly.

✓ Secondary Immune Response:

- This immune response occurs at the second and subsequent exposure of the same hot to same antigen.
- It is more rapid and stronger.
- It lasts for longer periods.

NON –SPECIFIC ACTIVATION OF IMMUNE SYSTEM:

1) Super- antigens

They are a class of antigens that cause non-specific activation of T-cells (They can activate up to 20% of T cells at one time) resulting in polyclonal T cell activation and massive cytokine release, which may lead to toxic shock.

2) Mitogens

- ✓ It is a **chemical substance** that encourages a cell to commence cell division, triggering mitosis. A mitogen is usually some form of a protein.
- ✓ Lymphocytes (B and T) can enter mitosis when they are activated by mitogens or antigens
- ✓ B cells divide to produce plasma cells when stimulated by mitogens, which then produce antibodies.
- ✓ Mitogens are often used to stimulate lymphocytes and thereby assess immune function.

- ✓ **In medicine** these proteins are useful and are used as a mitogen to trigger T-lymphocyte cell division
- ✓ The most commonly used mitogens in **clinical laboratory medicine are:**

➢ **1) Concanavalin A**
- ✓ **It is a plant mitogen, and is known for its ability to stimulate T-cell subsets**
- ✓ **ACTs upon T.cells**

➢ **2) Phytohaemagglutinin**
- ✓ **Found in plants**
- ✓ **Acts upon T.cell**

➢ **3) Pokeweed mitogen**
- **Acts upon both T and B cells**
- **Mainly works on memory cells**

➢ **LPS: lipopolysaccharide**
- **Acts upon B .cell**

• Regulation of Immune Response

{Negative regulation is critical for the termination of immune responses, and to avoid inflammation-induced tissue damage}

1) **Elimination of Antigen**:
- Antigens produce the immune response and their presence is what compels the response to go on so once they're removed, the driving force for the reaction is gone and the response can subside.

2) **Effecter elements**
- (Plasma cells, cytotoxic effecter cells, cytokines, antibodies ...) of the response are short-lived.

3) Expression of CTLA-4 : (cytotoxic T-lymphocyte-associated protein 4)
- After 2 or 3 days of activating T helper cells, they will express CTLA-4 on their surfaces and this is very similar to CD28 so the ligand for it is going to be B7
- It acts as an "off" switch
- CTLA4 is similar to the T-cell co-stimulatory protein, CD28, and both molecules bind to B7 on antigen-presenting cells. **CTLA4** transmits an **inhibitory signal** to T cells, whereas **CD28** transmits a **stimulatory signal**

- CTLA-4 function by capturing and removing B7 from the membranes of antigen-presenting cells, thus making these unavailable for triggering of CD28.

4) **IL-2**

- Too much of a good thing is a bad thing.Very good promoter of proliferation and growth of helper T cells but excessive exposure to high levels of IL-2 production would cause the cell to shut off in an attempt to suppress immune response.

5) Fas

- Receptor which can be detected on T -cells which have been activated for quite a while.
- Fas-L is its ligand and it's present on other T cells.
- When the ligand attaches to its receptor, it sends apoptotic signals to the cell.
- Sometimes the same cell produces Fas and expresses its ligand as if the cell is committing suicide

❖Antibody Feedback

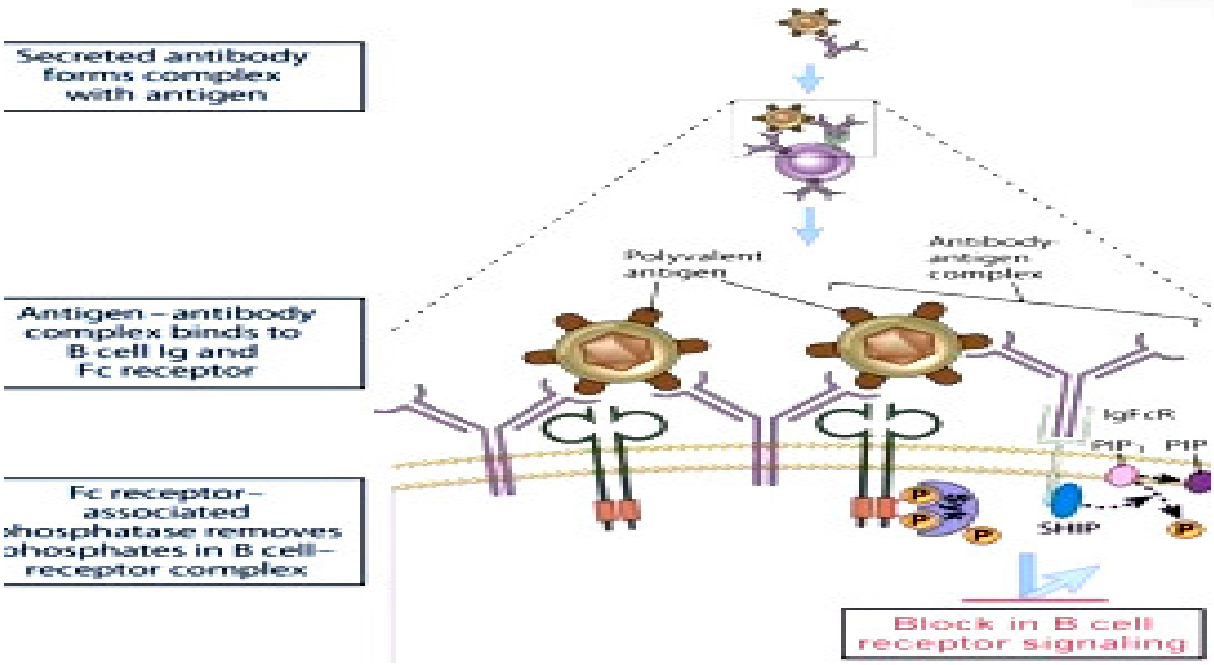
- Antibodies present on B cells which have BCRs and they also have Fc receptors.
- During the immune response, we produce antibodies and they're specific for antigens. We can actually join the immune complex to the B cell in two places
  1) The antigen can engage a BCR on the surface.
  2) The Fc part of the antibody (which is attached to antigen) can engage the Fc receptor on the B.cell

➢ Cross linkage of Fc and BCR by antigen-antibody complexes, the cell is actually shut off, cannot be activated.

➢ So when you have produced a lot of antibodies which are enough to interact with the present antigens, no more B cells are needed so you need to shut them off.

➢ **<u>Prevention of Rhesus immunization</u>** is an example of "antibody feedback inhibition". We use this to prevent B cells from being activated and producing Abs in cases of rhesus immunization.

➢ This mechanism is used clinically to prevent RhD-negative women from becoming immunized against RhD-positive fetal erythrocytes during pregnancy, we give the RhD-negative women antibodies against D.antigen, followed by antigen-antibody complex formation and interaction of this complex with any B.cell likely to produce antibodies against D.antigen; this interaction will cause inhibition of antibodies production.



يعطيكم العافية وموفقين بالامتحان

في خضم كل الأحداث المعاصرة ومن جوف الواقع الذي يفرض نفسه علينا , ثمة أمور مهما كان تأثرنا نحوها مندرج تحت بند التفاعل الانساني بالفطرة ولكن يجب ألا يغيب "التوجه المدروس " و"الواجب الذاتي السوي " عن أذهاننا , فتفاعلاتنا المكتوبة أو أصواتنا المنشودة هي مجرد عنصر اشباع مؤقت ,وكل ما ينطوي بعده من "عمل" هو المحرك الأساسي نحو الوصول لما عبرنا عنه مسبقا .