# DRUGS THERAPY IN DERMATOLOGY

**Prof. Dr. Khudair Al-Kayalli – College of medicine / Diyala University**

**Drugs therapy in dermatology is divided in to :- Topical and systemic therapy .**

## Topical therapy

**Topical** treatment offers the potential to achieve high concentration of a drug in the skin with minimal exposure of other organs , which can greatly increase efficacy and also safety relative to systemic administration .

**Prescribing** topical treatment requires careful consideration of **several factors** if optimal results are to be achieved , which include :-

1. **Concentration** of the drug .
2. **Type of vehicle .**
3. **Frequency of application .**
4. **Quantity to be used .**
5. **Precise site of application .**
6. **Precise timing of application in relation to bathing and other treatment .**
7. **Awareness of hazards associated with a topical therapy ( e.g. ICD , ACD ) and systemic absorption .**

**1. Choice of concentration :-** The efficacy of a topically applied drug is usually proportionate minimally with concentration and there may be also difference between adults and children . The prescribing conventions for specific concentration are usually written as **percentage** e.g. 1% = indicates that 1g of drug will be contained in 100g of the formulation ( vehicle ) , in liquid preparations 1% solution + indicate 1g of drug in 100ml of the formulation , **another convention** often used to describe the concentration of solution is in **parts** : thus 1part in 1000 solution of potassium permanganate contains 1g in 1ml of solution , which could be expressed as 0.1% ( w/v ) .

**2. Choice of vehicle :-** Topical medication must be applied to the skin in a suitable vehicle , the choice of vehicle depends on : **anatomical site** to be treated and the **condition of the skin .** As a role , acutely inflamed skin is best treated with fairly bland preparations , which are least likely to irritate . **Moist or oxidative eruptions** are conventionally treated with **'wet'** medications such as lotions or creams , while **dry skin** respond well to occlusive action of **ointments** , e.g. hair bearing skin , especially the scalp can be treated with medications formulated into shampoos , lotions , gels or mousses ( sweet or chocolate dish ) , oily skin affected by acne is often best treated with lotions .

**3. Frequency of application :-** The frequency of application must be specified in order to **maximize** the response and **avoiding** side effects such as irritation and unnecessary systemic absorption , for e.g. emollient should be applied frequently enough to maintain their physical effects . Active preparations are usually applied just once or twice a day , such as corticosteroids , because the pharmacological actions of such drugs may persist long after it has left the surface of the skin .

**4. Quantity to be applied :-** The total quantity to be dispensed should be specified and it is helpful to inform the patient how long the prescribed quantity is expected to last . The quantity of cream or ointment required for one week of once daily application to the whole body would be approximately 140g for male and 120g for

female , while twice daily applications requires 280g and 240g respectively . **The simple** practical guides to measure the quantity of topical medication to apply are :

**a. Finger tip unit –** it is an approximate but practical measure , it is the quantity of ointment extracted from a tube with a nozzle of 5mm diameter , that extends from the distal creases of the forefinger to the ventral aspect of the fingertip , which weights approximately 0.49g in male and 0.43g in female and covers about 300 square cm .

**b. The role of hand –** stats that an area of the size that can be covered by four adult hands ( including the digits ) can be treated by 1g ointment or 2fingertips unit , for e.g. the whole body of adult person requires 40 fingertips unit ( 20g ) .

**5. Hazards associated with topical treatment :- includes :**

**a. Localized irritant or allergic reactions .**

**b. Systemic side effects – as a result of absorption ,** which is enhanced by :

* Occlusion .
* Is greater in children and elderly .
* Hydrophilic drugs .
* Inflamed skin ( e.g. erythroderma ) .

**Formulation of topical therapy ( type of vehicle B.P. , U.S.P. ) :-**

* **Ointment –** is semi –solid vehicle composed of lipid , e.g. white soft paraffin BP ( petrolatum ) . They have useful , **occlusive** and **emollient** properties . Some ointments contain emulsifying agents such as polyhydric alcohols or cetosteraryl alcohols ( e.g. emulsifying ointment BP ) , the later have the advantage of being less greasy , with good solvent properties , and easily washed off . Ointment **required fewer preservative** than other vehicle because they contain no water and do **not sustain growth of microorganisms .**

* **Cream –** is semi-solid emulsions containing both lipid and water . Emulsion is suspension either of **lipid droplets in water ( oil in water O/W )** or of **water droplets in lipid ( water in oil W/O ) .** The former category ( **O/W )** is **aqueous** or vanishing cream ( e.g. aqueous cream BP ) it is : ***water miscible , * cooling ,* soothing , * and well absorbed into the skin .** The latter category ( **W/O ) is oily cream** ( e.g. oily cream BP ) it is : ***water immiscible , *difficult to wash of , *emollient , *lubricant , *mildly occlusive** ( but less than ointment ) .

* **Paste –** is semi-solid preparation containing a high proportion of finely powdered material such as zinc oxide or starch in lipid . It is of **two** types : **** Protective ( fatty ) paste –** is *** greasy , *missy , *water insoluble , * difficult to apply and remove , * occlusive , *protective and *hydrating ,** their stiffness permits accurate localization of the paste and any constituent medication . ****Drying ( cooling ) paste –** is mixture of powder with lipid ***non-greasy , *water miscible , *easy to apply and remove , *drying , * soothing and *can be used with dressing as paste bandages** or as vehicle for active medications . The consistency of the paste can be softened by adding oil or hardened with hard paraffin .

* **Lotion –** is liquid formulation that is usually simple suspension or solution of medication in water , alcohol or other liquids . Those containing alcohol often sting , especially when applied to broken skin . When the lotion left on the skin the liquid will evaporate leaving a film of medication on the surface . The aqueous suspension contains powder such as calamine , which require shaking prior to each application , so known as shake lotion .

* **Gel –** is thickened aqueous , semi-solid , lotion preparation containing high molecular weight polymers , such as carboxypolymethylene or methylcellulose . It is

***suitable for treatment of hairy areas , * dry when left on skin , *cosmetically acceptable for use on the face .**

* **Powder –** also known as dusting powder , is applied directly to the skin , **either inorganic powders** used to reduce friction ( tal**c** , zinc oxide , titanium dioxide , bentonite , and calamine ) **or organic powders** reduce excessive moisture ( various starch and zinc astearate ) , used as ***covering , *protective , *cooling , *soothing , *antipruritic , *UV reflectant** and occasionally used to deliver drugs such as antifungal agents applied to the feet .

* **Paint –** is liquid preparation , either **aqueous hydro-alcoholic** or **alcoholic (** tincture ) , which is usually applied by a brush to the skin or mucous membrane and then evaporate .

* **Collodion –** ( e.g. flexible collodion BP ) is liquid preparation consisting of cellulose nitrate in organic solvent , it evaporate rapidly to leave flexible film that can ***hold medications** in contact with the skin and most frequently used to apply salicylic acid and lactic acid to warts , also may be used as ***protective** to seal minor cuts and abrasions , ***easy to apply** and ***water repellent ,** but **inflammable .**

* **Microsponge –** it is a novel approach to formulation , involving the use of porous beads , typically 10-25um in diameter , forming a reservoir loaded with the drug , which provide sustained release of the drug while reducing irritation . It is used for **cosmetics** and **sunscreens** as well as for **medications** such as benzyl peroxide and retinoid .

* **Liposome –** is structure comprising aqueous phase surrounded by a lipid capsule , ranging widely in diameter from several nm to several um . It may contain several lipid layers so that the structure can be linked to that of onion , and under certain conditions liposome can release their contents close to the target cell and can be formulated in to creams and gels . It is used in **cosmetics** and in **dermatological treatment** to reduce irritation from topical use of retinoid , benzyl period and dithranol and reduce staining of the skin and clothes .

**The constituents ( gradient ) of formulation of vehicles ( BP , USP , BPC –codex ) are :-**

1. **Lipids –** are incorporated in to the vehicles , can act as **diluents** and **solvents ,** but are specially valuable as **emollients .** They have the ability to form a coating on the surface of the stratum corneum which inhibits evaporation of water , thus providing a softening and moisturizing effects . The sources of lipids are variable .

**2. Vegetable oils –** are largely composed of triglycerides with a large proportion of unsaturated fatty acids , such as oleic acid and linoleic acid which give unpleasant odor after oxidation , can be obtained from numerous vegetable sources by pressing or by solvent extraction , e.g. arachis oil , caster oil and olive oil .

**3. Mineral oils and greases –** are extract of crude oil ( crude petroleum ) can be produced as fluids , semi-solid or solid and include liquid paraffin BP , petrolatum USP . Because of their fully saturated nature , so they are more stable than the constituents of vegetable oils . They are remarkably inert and are not vulnerable to oxidation , so have pleasant odor .

**4. Lanolin ( wool fat ) –** is extracted from wool and is essentially the product of sheep sebaceous glands , so it is the choice of lipid material for use as emollient , it is miscible with water and is a useful emulsifying agent when mixed with other lipids .

**5. Fatty acids and alcohols –** long chin fatty acids , e.g. palmitic acid and astearic acid and their alcohols ( acetyl and astearyl ) are very frequently used as emollients and in creams as emulsifiers .

**6. Waxes –** beeswax is secreted by worker bees to make the cell wall of the honeycomb . It is composed mainly of free cerotic acid and myricyl palmitate and used as a thickening agent for creams , ointments and lip salves .
7. **Polyethylene glycols –** ( PEGS or macrogols ) are dihydric alcohols , they are polymers of ethylene glycol linked by ether bonds . At low molecular weight , up to 2000 they are ***hygroscopic** , so serve as **emollients , emulsifiers or thickeners** and can also be used to impart a **pleasant fell** or **texture** to formulation .

***Some formulations used in dermatology :-***

- ***Emulsifiers* –** an emulsion is a two phase system consisting of two immiscible components , the **dispersed** or **inner phase** being suspended in the **continuous** or **outer phase** as small droplets . One phase is **aqueous** and the other is **oily , W/O** system result from dispersion of an aqueous phase in an oily phase e.g. oily creams BP ( cold creams ) , the other is **O/W** oil in water system , is formed when oil is the dispersed phase and water is the continuous phase , as in aqueous cream BP ( aqueous or vanishing creams ) .
- ***Humectants* –** are compounds with a high affinity for water ( hygroscopic ) , they draw water into the stratum corneum and there for have an emollient effect on dry skin e.g. lactic acid and urea .
- ***Penetration enhancers* –** which enhance penetration of drugs through the skin include : propylene glycol , urea and dimethylsulfoxide , they acts by hydration of stratum corneum and keratolytic actions .
- ***Preservatives* –** are substances used to preserve creams , lotions and gels , because these vehicles contains accessible water , so easily contaminated by moulds and bacteria , they should be **non-toxic , non-irritant , non-sensitizing , odorless , colourless** and **effective** at very low concentration ( e.g. **parabens ) .**

## Some topical agents used in the management of skin diseases :-

***Antiperspirants* :-** are formulations that used to reduce sweat production and reduce axillary odor . Most of which marketed for cosmetic purposes contain **aluminum chloride hexahydrate** and often combined with antimicrobial agents that reduce axillary odor by inhibiting the action of bacterial metabolism on various component of apocrine sweat and fragrances are often added to mask or adjust the odor in various ways . In the treatment of **hyperhidrosis** of axillae , palms and soles higher concentrations of aluminum chloride hexahydrate ( e.g. 20-25% in ethanol ) are generally used as first line of treatment , they act by blockage of the sweat duct , applied once daily at night . Other antiperspirants are **aqueous glutaraldehyde solution** ( up to 10% as swab ) , **formaldehyde solution BP (**1-3% twice daily as soak ) . **Anticholinergic** agents orally inhibit sympathetic innervations of the sweat glands , which also can be used topically .

* **Astringents :-** are compounds used to reduce exudation acting by precipitation of protein which include :

**** *Potassium permanganate* –** as aqueous solution act as oxidizing agent with antiseptic and fungicidal activity , used in concentrations of 1/4000 – 1/25000 , it can be applied as a rinse , soak or as bath , 2g in 50liters of water give bath of 1/25000 , it stains the skin and materials .

**** Aluminum acetate ( Brow's solution ) –*** is mild antiseptic , not staining , the solution contains 55 aluminum acetate and is diluted 1:10-1:40 with water for use in soaks , rinses or wet dressing .

**** Silver nitrate –*** used in concentration of 0.1-0.5% , as an effective astringent and antiseptic , it stains the skin and materials .

## * Cytotoxic and antineoplastic agents :-

**** Bleomycin –*** cytotoxic with antitumor , antibacterial and antiviral activity , binds to DNA , used for treatment of viral warts ( intralesional injection of 1% bleomycin ) and oral leukoplakia as1% solution .

**** 5-Fluorouracil –*** is pyrimidine analogue , act as antimetabolite that inhibits pyrimidine metabolism and DNA synthesis , used as 5% cream ( 5-FU ) I treatment of multiple **solar keratosis ,** twice daily for two weeks topically , also used in **Bowen's disease , BCC , Viral warts , Paget's disease ( extramammarry )** and **Darier's disease .**

**** Diclofenac – is non-steroidal anti-inflammatory ,*** used topically for treatment of actinic keratosis ( 3% gel with 2.5% hyaluronic acid ) , act by inhibition of cyclo-oxygenase .

**** Podophyllin and podophyllotoxin –*** podophyllin ( podophyllum ) is a plant extract , traditionally used to treat genital wart , podophylotoxin is the most active constituent , they act as **antimitotic** , both should be **avoided in pregnancy , cause irritant reactions . Podophyllotoxin** 0.5% in ethanol ,or 0.15% cream , applied daily on 3 consecutive days each week to treat penile warts , **podophyllin 10-25%** in tincture of benzoin compound may be applied once or twice /week to genital or perianal warts , washed off after 6-12hours , 60-70% of genital warts clear with in 3-5 cessions .

## * Depigmenting agents :- are most frequently used for treatment of melasma

**e.g. *hydroquinone** used alone in concentrations usually ranging from 2-5% or in combination with retinoic acid in 0.025-0.1% . Also used in treatment of solar lintiginosis , applied at night for 3months .

***Monobenzyl ether of hydroquinone ( Benaquine )** usedas 20% cream used for treatment or bleaching of residual pigmented patches seen in vitiligo , to render the person white , by induction of permanent depigmentation .

***Mequinol** - is another phenol derivative with depigmenting properties , it is commercially formulated solution containing 2% mequinol and 0.01% retinoic acid , used for treatment of ***solar lentiginosis .***

***Retinoic acid ( tretinoin ) –** has been successfully used to reduce pigmentation : in **melasma , solar lentiginosis , postinflammatory hyperpogmentation** as 0.1% cream .

***Azelaic acid –** is dicarboxylic acid , mildly irritant , used as depigmenting agent in **melasma** by inhibition of tyrosinase , used as 20% cream , also used as **antineoplastic** , by inhibiting of DNA synthesis .

## * Corticosteroids :-

The basic corticosteroid structure molecule is hydrocortisone ( cortisol ) is introduced in 1952c . A numerous analogues have been developed from this molecule . Modification of both the ring and the side-chins have :

*** Increased specificity of action .**
*** Increased penetration .**
*** Increased potency .**
*** decreased side effects .**

**Hydrocortisone** has considerable mineralocorticoid activity , which can be reduced by **methylation** or **hydroxylation** at position 16 . **Esterification** at position 16 ,17 and 21 increased lipid solubility , which promote greater penetration of lipophilic

compounds ( e.g. betamethasone dipropionate and triamicinolone acetonide ) through stratum corneum . **Fluorination** of the 9alpha position , by introduction of florin molecule , increased potency ( fluorinated corticosteroids ) . The introduction of an saturated bond between the first two carbon atoms and changes in the nature of the side-chains , particularly in the 21postion , brought about enhanced **glucocorticoid** activity .

It is essential for dermatologist to be able to rank or classify different corticosteroid by **potency** in order to predict the response and possible **adverse effects** . The classification of potency of topical steroids is based on the **vasoconstrictor assay** and other evidence such as comparative clinical trials . The **British National Formulary** employs **four-point scale (** mild , moderate , potent and very potent ) , and in the **USA ,** the topical corticosteroids are ranked using a scale ranging from class 1 ( super potent ) to class 7 ( mild ) .

***Mechanism of action :***

a. **Anti-inflammatory activity through Suppression of production of inflammatory cytokines , inhibition of T-cell function , changes in the function of endothelial cells , granulocyte , mast cells and fibroblasts .**
b. **Inhibition of proliferation .**
c. **Vasoconstrictor activity .**
d. **Immunosuppressive .**

***Side effects of topical corticosteroids :-***

1. **Skin atrophy and telangectesia –**may be permanent on epidermal cells and derma collagen .
2. **Promoting infections –** bacterial , viral , fungal and parasitic .
3. **Contact allergy –**to steroid and preservatives .
4. **Acneforms eruptions ( steroid acne ) and rosacea like eruptions , perioral and periocular dermatitis .**
5. **Risk of systemic absorption , with inhibition of pituitary – adrenal axis , DM , hypertension and skeletal disorders .**
6. **Localized hypopigmentation ( due to inhibition of melanocyte ) .**
7. **Cataract and glaucoma .**
8. **Impair wound healing and reepithelization .**

**Corticosteroids** are used topically as cream , ointment , lotion , gel or mousses and may be used alone or in combination with antibiotic or antifungal drugs ,under occlusion or as intralesional injection .

***Retinoids :-** can be defined **either** as compounds related structurally to retinol ( vitamin A ) **or** as compounds that are able to interact with retinoid receptors ( which become the more useful definition ) , as a result of increasing number of synthetic retenoids . Retenoids act by ***regulation of cell differentiation** and **proliferation ,** and used in treatment of : **acne , psoriasis , photoaging , disorders of keratinization , as well as for suppression of dysplasia and malignancy .**

The activity of endogenous retinoids within the cell is regulated by binding proteins known as **cellular retinol binding proteins (CRBP one and two** ) and **cellular retinoic acid binding proteins ( CRABP one and two )** , these proteins are widely distributed through out the body in many cell types ,CRABP two predominates in skin , and is found in keratinocytes and fibroblasts . Systemic retenoids are known to be highly **teratogenic** , so they should be **avoided during pregnancy** , even the topical use **. The retinoids include :-**

***Retinol ( vitamin A ) –** is one of the naturally occurring endogenous retinoid , which is metabolized within most cells to retinoic acid , and used widely in cosmetic products and tends to be regarded as a vitamin supplement rather than a medicament , topically applied retinol is absorbed into the epidermis , so increases epidermal thickness , but cause much less irritation , it is used as 10% gel as a component of depigmenting regimen .

***Retinoic acid ( tretinion , vitamin A acid )** – is most frequently used in treatment of **acne vulgaris ,** applied once or twice at a concentration of 0.01-0.025% in a lotion , cream , or gel and 0.1% in the past , also used in **photo-aging skin tumours , psoriasis , melasma , promote wound healing , senile comidones , plane warts ,Darier's , keratosis pilaris , lamellar , iccthyosis , oral lichen planus , keloid and hypertrophic scars .**

***Isotretinoin ( 13-cis retinoic acid )** – is readily isomerized to tretinoin so has similar receptor specificity to tretinoin . It is used topically and systemically for treatment of **acne vulgaris** topically less irritant than tretinoin but may be more so than adapalene , used as 0.05% gel ( isotrex ) , also used in **photo-aging , anti-neoplastic , BCC , oral and vulval leukoplakia , oral LP , melasma , and Darier's** ( act by inhibition of comedogenesis and decrease sebum secretion .

***Adapalene –** is a synthetic retinoid , that have been developed for treatment of **acne vulgaris ,** as 0.1% gel . it is equally effective , less irritant than 0.025%retenoic acid gel , and slightly more effective and less irritant than topical isotretinoin , it is used as gel , cream , and lotion as a single daily application ( **it is comedonolytic and anti-inflammatory ) .**

***Bexarotene –** is a novel synthetic retinoid with specificity for retinoid receptors , it has proved helpful in the treatment of **cutaneous T-cell lymphoma ,** as gel up to 1% , 4times /day for 20weeks .

***Tazarotene –** is a synthetic retinoid used topically for treatment of **psoriasis** and **acne vulgaris** , also used orally for treatment of psoriasis , topically as 0.1% gel and cream , once daily , also used in **psoriatic onycholysis , nail pitting , photo-aging , oral Lp , keratosis pilaris , ichthyosis , Darier's disease , pseudoacanthosis nigricans .**

* **Sunscreens :-** are compounds can **reduce UV exposure** and probably the risks associated with **photo-aging** , notably **neoplasia .** The **idea**l sunscreen should be :-

**1**. Completely block the transmission of both UVB ( 280-315nm ) and UVA ( 315-400nm ) .

**2.** Cosmetically acceptable .

**3.** Pleasant to use .

**4.** Water resistant .

**5.** Long durability on the surface of the skin .

Sunscreens are generally more effective in blocking UVB than UVA , and fall in **two broad categories :**

a. **Physical sunscreens –** which act by **reflecting** and **scattering** of visible and UV light , e.g. zinc oxide , titanium dioxide and ferrous oxide (UVB &UVA).
b. **Chemical sunscreens –** which act by **absorbing** of UV light , e.g. para-aminobenzoic acid ( PABA ) and it's derivatives ( block UVB ) , anthranilates ( UVA ) , cinnamates ( UVB ) , benzophenones ( UVA ) , and camphor derivatives ( UVA ).

***Vitamin –D analogues :-** used in the treatment of **psoriasis** , topically and systemically ( cause disturbance of calisiom homeostasis ) , e.g. calcitriol , calcipotriol , tacalcitol and maxacalcitol .

* **Immunomodulators :-** are topical medications alter immune response , used for treatment of atopic dermatitis e.g. ***tacrolimus** , which is a macrolide lactam antibiotic , also used in psoriasis ( 0.1 and 0.3% ointment twice daily ) .
***Pimecrolimus –** also macrolactem used in atopic dermatitis .
***Ciclosporin –** is used in erosive lichen planus .

## Systemic therapy

**Systemic therapies are introduced via :-**

a. **Oral rout .**
b. **Intramuscular rout .**
c. **Intravenous rout .**
d. **Percutaneous rout .**

* **Corticosteroids :-** Indications in dermatology are :

1. Acute self limiting steroid sensitive disorders e.g. acute ACD .
2. Acute anaphylactic reactions e.g. following a bee or wasp sting .
3. Acute autoimmune connective tissue diseases and generalized immunological vascular disorders e.g. SLE , dermatomyositis , polyarteritis nodosa , giant cell arteritis , Wegener's granulomatosis .
4. Chronic disabling immunological bullous diseases e.g. pemphigus vulgaris , pemphigoid .
5. Acute generalized exfoliative dermatitis e.g. resulting from a sever drug reaction .
6. Miscellaneous disorders , e.g. sever lichen planus , pyoderma gangrenosum and sarcoidosis .
7. In a group of skin disorders , although systemic steroids are used , but the value of such treatment is unproven e.g. EM , Stevens-Johnson syndrome , TEN , chronic urticaria and cutaneous T-cell lymphoma .

**Routs of administration of corticosteroids :-**

a. **Intravenous ( IV ) –** is useful in emergency treatment of acute anaphylaxis and in pre-and postoperative cover of patients who have previously been received systemic steroid for 4weeks or more ( given 25mg hydrocortisone at time of induction of anesthesia , 100mg during the operation and 100mg on the first postoperative day .
b. **Intramuscular ( IM ) –** e.g. triamicinolone , is popular in the USA for systemic steroid administration for short term less than 4weeks treatment . This drug dose not differ significantly from prednisolone in its short –term action , but in long term it possesses greater mineralocorticoid activity .
c. **Pulsed steroid therapy –** this is usually administered as doses of 1g of methylprednisolone given IV over several hours using an IV line , the dose can be repeated daily for up to 5days . It may be indicated in patients with sever bullous dermatoses , especially pemphigus vulgaris , it is a potentially hazardous procedure , and thromboembolosm , cardiac arrest and steroid psychosis are occasional complications .
d. **Oral steroids –** may be taken in a single daily dose or used on alternate –day regimen .

***Single daily dose :** is used for short –term systemic steroid therapy , it should be given firstly in the morning , because of diurnal rethyme to avoid hypothalamus-pituitary-adrenal suppression .
***Alternate day dose – given twice the daily dose of steroid .**

**Systemic side effects :-** osteoporosis , diabetes mellitus , hypertension , glaucoma and cataract .

## * Sex hormones and related compounds :-

***Androgens :-** Testosterone is the most potent androgen and is currently only used for replacement therapy , many derivatives of testosterone have been developed called ***anabolic steroids*** , because of prounced ***anabolic action ,*** and often troublesome ***virilizing activity .***

*** Anabolic steroids :** Include : ****Danazol- ( 100-600mg/day )*** is synthetic steroid derived from *ethisterone , with high affinity for androgen receptors and although itself a week androgen , it has :*

***a. Marked antiandrogenic activity .***

***b. Inhibits gonadal steroid production .***

***c. Reduce secretion of FSH and LH by the pituitary gland .***

***d. Increase hepatic synthesis of C1 esterase inhibitor and antitrypsin ,*** so it is of great value in the treatment of : **** Hereditary angio-edema .**

**** Cholinergic urticaria , which resist antihistamines ( due to antitrypsin ) .**

**** Autoimmune progesterone dermatitis .**

***e. It is hepatotoxic .***

****Stanozol- ( 2.5-10mg/day )*** is also a potent anabolic steroid with mild virilizing activity , used in :- ****Hereditary angioedema , ** has marked fibrinilytic activity ** cheaper than danazol ,** with **similar side effects .**

*** Antiandrogens :-** Are drugs with antagonist action to the androgen , although they related structurally to different groups , which include :

1. ***Cyproterone acetate* –** it is a potent antiandrogen that competes with androgen at receptor's sites , and inhibit gonadotrophin secretion . In a low dose ( 2mg/day ) , usually in combination with **ethinylestradiol (** 12.5-50ug ) , are used for treatment of ***acne , * hirsutism , * other virilizing diseases in females , *hepatotoxic , *contraindicated in pregnancy .**

**2.** ***Spironolactone ( aldactone ) –*** blokes androgen receptors , but at low dose , it is less effective than other antiandrogen , high dose 200mg/day is very effective , which cause dysfunctional uterine bleeding ( controlled by oral contraceptive ) , used in hirsutism .

**3.** ***Flutamide* –** also blocks androgen receptors and at dose of 250-500mg/day for 6months , may be effective in treating hirsutism **, dry skin** ( very frequent ) and **hepatotoxicity** are possible with high dose .

**4.** ***Finasteride* –** is a 5-alpha –reductase type2 inhibitor that blocks conversion of testosterone to dihydrotestosterone in the skin , it is less effective as antiandrogen , but a dose of 5mg/day may decrease **hirsutism** without adverse effects , and at dose of 1mg/day it produce clinical improvement in up to 66% of men with **androgenic alopecia** treated for 2years .

***5. Histamine-2 receptors antagonist*** –e.g. cimitedine .

***Oestrogens :-** are female sex hormones , used to ****prevent skin aging , *treatment of autoimmune progesterone dermatitis*** , ( e.g. **ethinylestradiol 10-35ug/day )** as ****replacement therapy for post menopausal symptoms*** **(** including : hot flushes , vaginal atrophy ) , it should be avoided in patients with a history of **: breast cancer , liver and thromboembolic diseases .**

***Anti-oestrogens :-** ****Tomoxifen – ( 20mg/day )*** it acts at receptor's sites to block oestrogen binding – so inhibits ovulation in fertile women , useful in treatment of ***progesterone- induced dermatitis or erythema multiforme ,*** side effects are those associated with **menopause** and **abnormal vaginal bleeding .**

***Antihistamines :-** Are drugs that acts on histamine receptors , and block histamine release . There are four types of histamine receptors :

***H1-** expressed on skin cause , vasodilatation, vasopermeability, and itching ,e.g. chlorphenarmine and terfenadin .

***H2-** expressed on skin cause , vasodilatation ,vasopermeability ,e.g. cimetidine , ranitidine .

***H3-** expression on skin is suspicious cause , regulation of histamine–neurotransmitter release , e.g. thioperamide .

***Hic-** expression on skin is suspicious , act as intracellular messenger for promotion of cell growth , e.g. DPPE-diethyl-phenyl-methyl-phenoxyl Ethanamine ( experimental diagnosis ) .

**As** well as to anti-histamine action , most of H1anti-histamines expresses **anti-cholinergic activity** , resulting in : *dryness of mouth , blurred vision , constipation , drowsiness and sedation* .

**Ketotifen** and **cetirizine** are anti-H1 , which have a potent inhibition of release of mast cell products ( so used as prophylactic therapy ) .

**A. H1 anti-histamines :** include :

**1. First generation H1 anti-histamines –** are a potent anti-histamines , but accompanied by troublesome atropine –like side effects and also cause drowsiness , which include :

***a. Alkyl amines* –** e.g. chlorphenarmine ( polaramine 4mg/d ) , plasma half life ( PHL ) is approximately 24hours .

***b. Amino alkyl-ether* –** e.g. diphenhydramine ( allarmine 25mg-2/d ) , PHL is 9hours .

***c.Piperazine , e.g. Hydroxyzine*** ( aterax 10-25mg/d ) , PHL is 20 hours .

***d. Phenethiazines* –** e.g. promethazine , PHL is 12 hours .

***e. Ceproheptadine ,e.g. Periactine .***

***The peak plasma concentrations** are reached in approximately 2hours .

***Protein binding** is almost total .

***Metabolism** occurs via the **hepatic microsomal cytochrome P-450 system ,** thus the half life of certain H1 anti-histamine may be prolonged in patients receiving microsomal oxygenase inhibitors such as ***ketoconazole , erythromycin , doxepin and cimitidine .***

***They acts by** causing vasoconstriction , decrease vasopermeability , thus reducing redness , weals , and axon reflex flare reactions in urticaria , **once daily** , is therefore adequate , it alleviate itching due to **sedative effects** , so used in atopic dermatitis .

***The side effects** are those of anti –cholinergic effects , *tachycardia , prolongation of Q-T interval on ECG and other arrhythmias* , as well as *psychological disturbances* .

**2. Second generation H1 anti-histamines :-** are non-sedative , because they do not significantly cross the blood -brain- barrier , the absorption and metabolism resemble that of the first generation anti-H1 , they include :

***a. Terfenadine-*** has no anti-H2 and anti-cholinergic activities , effective in the treatment of **chronic urticaria .** Agents and drugs which inhibit hepatic metabolism via the **cytochrome P-450 system** , should not be given concurrently with terfenadine , because they may promote adverse effects including : ***cardiac arrhythmias , *Q-T interval prolongation , *ventricular tachycardia ,** also contraindicated in **liver and heart diseases** ( e.g. grapefruit juice , ketoconazol , itroconazol , erythromycin and other macrolides , cimitidine , doxepin ) , also may cause skin rash , so due to this adverse effects , it is replaced by its major active metabolite ( fexofenadine ) .

***b. Astemizol* –** also undergoes first-pass metabolism via the **liver cytochrome P-450** system , but it's half life together with it's metabolite ( dimethyl-astemizol is

prolonged at 9.5 days . It has histamine weal suppression , being evident 4weeks or more after discontinuation , increase appetite – so excessive weight gain , but **not to be teratogenic ,** the **adverse effects and contraindications are like terfenadine .**

***c. Loratadine* –** is a potent , but minimal sedation anti-histamine , free of anti-cholinergic side effects , but **not metabolized through liver cytochrome P-450 system ,** and there fore believed free of cardiac arrhythmias complications . **It inhibits release of leukotrienes ,** so used as anti-allergic , in UK it has been replaced by desloratadine .

***d. Cetirizine* –** like loratadine , it is an active metabolite of hydroxyzine , is only minimally metabolized via the liver , and there for can be administered safely with macrolides , imidazole , doxepin . It is claimed to be effective in diseases involving **heavy eosinophile infiltration** e.g. **physical** and **pressure urticaria .**

**** H1 – anti-histamine in children –** second generation are probably **safe** , than the older classic first generation , which in over dose may cause sever toxicity , including **hyperpyrexia and convulsions .**

**** H1-anti-histamine in pregnancy – non** of anti-histamine administered systemically , should be deemed **safe , in the first trimester** of pregnancy , ***but*** chlorphenarmine ( polaramine ) and tripelennamine ( Actifed ) have shown little or no evidence of teratogenicity experimentally .

**** H1-anti-histamine** user may develop tolerance during therapy , e.g. hydroxyzine 75mg given daily for 3weeks may cause tolerance , but no tolerance developed to chlorphenarmine 16mg/day for the same period .

**B. H2-anti-histamine :-** Although H2-receptors are predominantly seen in the GIT , but these receptors are expressed on human skin blood vessels **, so they** co-administered with H1-anti-histamine , in the treatment of **chronic urticaria** , to minimize unwanted first-generation H1-anti-histamine side effects , like drowsiness and atropine –like side effects . **Ranitidine** unlike **cimitidine** is not metabolized via liver cytochrome P-450 system , so it should probably be used in preference to cimitidine if H2-anti-histamine therapy is instituted .

* **Cytokines :-** Are small polypeptides , with molecular weight less than 60KDa , which acts as intercellular messengers , they have a pivotal role in cutaneous inflammation , they can be either **pro-inflammatory or anti-inflammatory ,**so used in treatment of skin diseases .

* **Interferon's :-** Are naturally occurring endogenous glycoprotein's , which are now available for therapeutic use through recombinant DNA technology .They exhibit **antiviral , cytotoxic** and **immunomodulator** properties , so used in **malignant and inflammatory skin diseases .** Three types of interferon are available ( IFN alpha, beta and gamma ) , unfortunately side effects are common including : **influenza-like symptoms with fever , hepatotoxicity** and **leucopenia ,**which limit clinical usage . They are used in treatment of – **Kaposi's sarcoma , melanoma , cutaneous T-cell lymphoma and atopic dermatitis .**

* **Interleukins :-** Are an expanding group of endogenous soluble mediators , used for treatment of inflammatory dermatosis , malignancy and infections .IL-2 is the most commonly used for therapy of **melanoma . In psoriasis** ( Th1-mediated diseases ) , there fore systemic administration of Th2 –cytokines , such as IL-4, IL-10 or IL-11 are used .

* **Cytokine blocking agents :-** By DNA technology , the production of neutralizing or inhibitory antibodies to pro-inflammatory cytokines , are used for

treatment of inflammatory diseases e.g. Rh- Arthritis , Crohn's disease and psoriasis , e.g. TNF- alpha blocking agents ( infliximab and etanercept ) .

*** Retinoids :-** They includes both the synthetic and natural forms of vitamin A ( the term vitamin A includes : the performed vitamin A –alcohol , retinol , it's aldehyde , retinal , and it's acid , trans –retinoic acid , as well as the provitamin B-carotene ) . The **mode** of action has not been completely elucidated , but they have profound effects on differentiation , cell growth and immune response , so used as :

***** They effects cell differentiation and as keratolytic .

***** Anti-carcinogenic by inhibition of **ornithin decarboxylase enzyme .**

***** Inhibition of human tumour cell growth e.g. **melanoma .**

***** They effects cell surfaces and lead to loss of anchorage-independent growth , cell adhesiveness and density dependent growth .

***** They acts as immunostimulant , there fore they stimulate antibodies formation to antigens ( that were previously not immunogenic ) , and also stimulate cell mediated cytotoxicity , and reduced neutrophil migration . **They are :**

**a.** ***Isotretinoin( 13-cis-retinoic acid )*** **–** is used in treatment of *****recalcitrant cystic acne unresponsive to antibiotic , dose 0.1-2mg/kg/day ( mostly 1mg/kg ) for 16weeks *****Gram-negative folliculitis , ***rosecea ,** and ***hydradenitis supurativa ,**half life 30days .

**b.** ***Etretinate*** **–** the half life is 120days , and the major disadvantages it's binding to body fat for up to 2years after the course has been completed , used in **psoriasis ( tigason )** , nowadays it is replaced by acitretin .

**c.** ***acitretin*** **–** is the active metabolite of etretinate , it's elimination half life is 2days , less bound to fat than etretinate . It is effective in various forms of ***psoriasis ,** especially pustular types and erythrodermic , ***disorders of keratinization** e.g. **keratoderma , X-linked ichthyosis , ichthyosis vulgaris , PRP , DLE, LP, Darier's disease , * skin tumours** e.g. **solar keratosis , keratoacanthoma ,BCC,** and **leukoplakia .**

**d.** ***Bexarotene*** **–** is synthetic third generation oral retinoid , under development , used for treatment of **cutaneous T-cell lymphoma ,** 300mg/squer miter/day , may cause hypertriglyceridaemia (79%) and central hypertension .

****<u>Side effects of retinoid :</u>**

1. On skin cause chelitis , dryness of mucous membrane , desquamation of hands and feet , pruritis and alopecia .
2. Conjunctivitis , epistaxis .
3. Myalgia and arthralgia .
4. Intracranial hypertension ( avoid combination with tetracycline ) .
5. Increased hepatotoxicity of methotrexate .
6. Depression and suicidal intention .
7. Abnormal liver enzymes .
8. Increased VLDL ( very low density lipoprotein ) , cholesterol and reduction of HDL ( high density lipoproteins ) .
9. An ossification disorders ( DISH ) disseminated idiopathic skeletal hyperostosis .
10. Teratogenicity – 100% teratogenic , so it is important that womens are not pregnant prior to starting treatment and effective contraception is mandatory during and after a course of treatment ( in isotretinoin for 3months , in etretinate for 2years and in acitretin for one month ) , **males** can safely father children ( even during therapy ) .

## *Immunosuppressive and cytotoxic drugs :-

Those drugs which are primarily used in oncology now may be of value in dermatological practice include:

1. **Alkalating agents –** they acts by alkylation of DNA when cells enter the S phase , leads to impaired replication .

***Cyclophosphamide-*** dose 1-3mg/kg in 2-3 divided dose , anti-mitotic and immunosuppressive , used with corticosteroids for the treatment of **pemphigus , pemphigoid , SLE, polymyositis , mycosis fungoides** and **histosytosis-X .**

***Chlorambucil-* dose 0.1-0.2mg/kg/day** , in one or two divided dose . slow acting , less toxic than cyclophosphamide , used for treatment of **mycosis fungoides , Behcet's syndrome , SLE ,Wegener's granulomatosis , steroid resistant sarcoidosis , Sezary syndrome** with prednisoline .

***Dacarbazine* –** dose 2-4.5mg/kg/day , IV for 10days , it is imidazol derivative , mode of action is unknown , used particularly for the treatment of metastatic malignant melanoma .

2. **Anti-metabolites :**

***Methotrexate* –** it is structural analogue of **folic acid** , and is a potent competitive inhibitor of dihydrofolate reductase , which convert dietary folic acid via dihydrofolate to tetrahydrofolate , so inhibit nucleic acid synthesis and cell division . It acts as antimetabolite and anti-inflammatory , used in the treatment of sever **psoriasis ( pustular , erythrodermic and erythropathic ) in dose 0.2mg/kg/week** , in 3divided dose 12hours apart , **in cutaneous sarcoidosis , dermatomyositis , DLE , systemic sclerosis , morphea , atopic dermatitis , Behcet's syndrome , polyartritis nodosa , small vessels vasculitis , pyoderma gangrenosum , pityriasis lichenoides , bullous pemphigoid , pemphigus .** It required normal haematological , hepatic and renal functions .

***Azathioprine ( immurane)-*** it is converted in the body to 6-mercaptopurine (6-MP) , originally used in transplant surgery . 6-MP **inhibits purine synthesis** , **immunosuppressive** and **anti-inflammatory** used in : **dermatomyositis , SLE, DLE , PV , BP , AD , chronic actinic dermatosis , Behcet's syndrome , vasculitides , pyoderma gangrenosum , psoriasis , PRP . the dose is 1-3mg/kg/day ,** usually used as steroid –sparing agent .

***Bleomycine* – is** a polypeptide antibiotic given parentrally , has no immunosuppressive action and it's toxicity is confined to the skin causing hyperpigmentation , and inflammatory lesions especially on the palms and fingers , also effects the lungs . It is used in : **SCC , MF , other lymphomas .**

***Hydroxyurea* – dose 500mg 2-3times/day ,** it blocks pyrimidine synthesis , causing much more short-term marrow suppression than methotrexate , but less effective than methotrexate and has little effect in psoriatic arthropathy , easy administer , inexpensive , with few contraindications or side effects , and may cause dermatomyositis like rash and leg ulceration .

**3. Cyclosporine :** is a cyclic polypeptide made of 11amino acids , the main **mode of action** is on : a. Helper-T cells , which blocks the cell cycle in G0 or early G1 .

b. Inhibit production of various lymphokines notably IL-2 .

c. Have some direct effect on DNA synthesis and on proliferation of keratinocytes .

**It is used** as ***immunosuppressive in organs transplant** e.g. kidneys , liver , heart , bone marrow , ***Rh-arthritis , SLE, dermatomyositis , psoriasis ( PPs, ArP ) ,** dose 3-5mg/kg/day for 1-3months . Also used in ***AD, PV, BP, pyoderma gangrenosum** and **chronic idiopathic urticaria .** It has little toxicity on the boon marrow or liver ,

but have considerable and large reversible toxicity on the kidneys an increasing blood pressure .

*__**PUVA:-**__ Is photochemotherapy with 8-methoxypsoralen followed by UVA radiation for psoriasis , 5-methoxypsorale can be substitute 8-MP . **PUVA** is also of value in **MF, sever AD in selected children** ( mean age 11.2years ,2/week ) , **hand eczema , nodular prurigo , vitiligo , LP, granuloma annular , urticaria , idiopathic pruritis , urticaria pigmentosa . PUVA** therapy may accelerate the development of **skin tumours e.g. SCC,BCC, and melanoma .**

*__**Photopheresis -**__ Extracorporeal photoimmunochemotherapy ( **ECP )** is derived from **PUVA** therapy , which involves the extracorporeal exposure of peripheral blood mononuclear cells (**BPMC**) to 8-methoxypsoralen and UVA radiation before being returned to the patient . **ECP** photopheresis most widely used on 2successive days , repeated at 2-4weeks intervals , the exact **mechanism of action** is not fully understood , but it is believed that the patient's immune system is stimulated to destroy the **altered and/ or damaged malignant T-cells of cutaneous T-cell lymphoma ,** also ECP is used as palliative treatment of **Sezary syndrome** and also used in **systemic sclerosis , SLE, AD, PV,** and **ArP .**

*__**Plasmapheresis ( plasma exchange ):-**__ Has been used in patients with sever **SLE** which failed to be controlled by high-dose of corticosteroids and immunosuppressants , also life-saving in **sever lupus nephritis , Good pasture's syndrome , dermatomyositis , PV, BP . Between** 7-14theraputic plasma exchange are required , the main side effect is **hypertension .**

*__**Intravenous immunoglobulin therapy ( IVIG ) :-**__ Ig is produced from pooled human plasma , it has been used in treatment of variety of **autoimmune bullous** and **inflammatory dermatoses .** High doses (1-2g/kg) are recommended , usually delivered as a 5conseccutive day cycle of 0.4mg/kg/day , each infusion is given over 4-4.5hours , initially the cycles are repeated every 3-4weeks , until there is effective control of disease , once this has been achieved , the time intervals between the cycles can be gradually increased , an end point is two infusions of 16weeks apart . **The side effects are :** headache , chills , flushing , vomiting , aseptic meningitis , thrombosis , anaphylaxis , and risk of infections e.g. HIV . It is used **PV** 2g/kg , **BP , EB** and **TEN .**

*__**Physical therapies :-**__

**1. Cryosurgery** - is freezing of the skin , which is achieved by : **salt-ice mixture -20deegre centegret , CO2 snow -79C , diethyl ether and propane ( histofreezer -50C ) , nitrous oxide -70C and liquid nitrogen-96C** , the lowest temperature , work the faster . Liquid nitrogen works faster , easy to use , inexpensive , readily available , so commonly used . **Cryotherapy** is believed to cause cell death by :

a. Ice crystals formed in the cell .

b. Uneven intracellular ice formation during freezing leads to osmotic differences arising during thawing , which in turn cause cell disruption .

c. Cold injury to small blood vessels results in ischemic damage .

d. Immunological stimulation produced by the release of antigenic components results in cell damage .

Maximum damage is produced by ***rapid freezing ,*slow thawing , *repeating the freeze-thaw cycle .** It is suggested that the temperature of -30C is required to produce cell death . **Cryotherapy used for treatment of : pigmented and epidermal naevi , lentigo , telangiectasia , vascular lesions , spider naevus , pyogenic granuloma ,**

**viral warts , pseudopyogenic granuloma , Kaposi's sarcoma , haemangioma and lymphangioma , MC , seborrheic keratosis , solar keratosis , cutaneous horn , keratoacanthoma , Bowen's disease ,BCC, SCC, lentigo maligna , cysts , leukoplakia , axillary hyperhydrosis , keloid , acne scare , sebaceous hyperplasia and rhinophyma .**

The side effects are : pain , swelling , haemorragic blisters , hypopigmentation , hyperpigmentation , paraesthesiae and scaring .

2. **Curettage –** is done by using curate , used for fragile skin lesions e.g. BCC , or there is a natural cleavage plane e.g. seborrheic wart , viral wart , PG, solar keratosis , SCC, Bowen's disease .

3. **Electro-surgery ( diathermy ) –** Which includes : ***electro-desiccation*** ( has unipolar electrode , needle contact the skin , no spark ) **,** ***electro-fulguration*** ( needle contact the skin with spark ) ,***cutting diathermy*** ( electro-section or electro-resection ) , and ***electrolysis , also electro-cattery*** is involved in this topics , weather it is electrical or hot oils or cattery irons .

***Electro cattery ( cattery, heat cattery , hot-wire cattery )*** – in this technique the tip temperature can be adjusted , and a variety of tips are available , cause scaring and required anesthesia .

***Electrolysis –** hair removal , which can be achieved by electrical current reaches the germinal bulb via a needle inserted to the correct depth .

**4. Infrared coagulation -** produced by ordinary light ( non-coherent ) , with a spectrum of 400-700nm , which produce heat causing thermal injury to a depth dependent on the duration of exposure .

5. **Caustic and chemical peeling –** caustics provide a simple and readily available means of destroying many superficial skin lesions e.g. ALCL –hexahydrate ( 20%solution) , silver nitrate , TCA ( 30-50% solution ) , phenol ,DCA, MCA ..

**6. Laser and flash lamp ( intense pulsed light sources ):-( light amplification by stimulation of emission of radiation ) .**

***First laser** initiated in 1959 – Ruby crystal –wave length 644nm –used for tattoos and hair removal .

***Neodymium –Yttrium –Alaminium-Granet Laser ( Nd:YAG532-1064nm) - 1961**: used for tattoos , Port-wins , malignancy .

***Argon laser -1962-**used for vascular lesion .

***Co2 laser -1964 .**

***Selective photothermolysis -1983 –**used target chromophores ( such as haemoglobin and melanin ) , for the treatment of superficial malformations , tattoo and benign pigmented lesions .

***Flash lamp technology ( recent ) –**produces high-intensity pulsed light in the 410-1200nm ( VPL,IPL) , used for hair removal , pigmented lesions , and telangiectasia .

**Various** safety measures are required to prevent accidents , resulting from exposure to direct or reflected beams , which includes : ***removal of inflammable materials , * damage to skin or eyes , * inhalation of plume .**

**The generic name** of a laser reflects the component of the solid , liquid or gas that constitutes its active medium and determines the wave length(s) of the radiation produced . The beam may be **continuous , pulsed** or **quality switched (Q-switched).**

***Continuous wave light –**is a constant beam and has relatively low power .

***Pulsed wave light –** is interrupted to produce pulses with higher peak power than in continuous mode and to allow cooling between pulses ( **Pulsed dye laser 585-600-**used for vascular , pigmented lesion , keloid and hair removal e.g. port-wine .

***Q-switched –**is creating a very short pulse (nanosecond) with high peak power .