



## CENTRIFUGAL PHARMACOLOGY AND RELATED TOPICS

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Article Received on: 11/01/2024

Article Revised on: 01/02/2024

Article Accepted on: 21/02/2024



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Pharmacology and Pharmacy,  
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The modern pharmacology relies on the action enforced by the drugs on the body. The new therapeutic approach proposed here is based on the opposing reaction initiated by the body in response to the initial action of the drug. The former can be considered as primary, afferent or centripetal pharmacology and the later as secondary, efferent or centrifugal pharmacology. The centrifugal pharmacology concept is examined with the prospect of expanding the therapeutic application of a given drug. The proposed concept opens up new avenues of therapeutic discoveries outside the costly standard drug discovery protocols. In order to understand the new therapeutic dynamics, an early classification of drug actions in relation to diseases, the concept that the drugs are another form of disease forces and that the drug actions are either dose dependent or dose independent are discussed. The new concept can be applied even by individual practitioners to already approved drugs for possible new therapies and does not incur huge costs needed in the discovery of new drugs. The proposed system demands an extra effort in case taking and in the selection of the indicated drug. The responses are subjected to greater biological variations than those of modern drugs and the new system is not suitable in acute life-threatening conditions.

**KEYWORDS:** Ardent-Schultz rule, hormesis, iatrogenic diseases, micro dosing, clinical trials Phase – 0, collective intelligence.

**INTRODUCTION**

The article intends to bring to focus a new dimension in pharmacology and therapeutics of medicinal agents. Centrifugal pharmacology operates under all forms of stimulating forces be it motion, temperature, radiation, chemical or emotional. There is said to be a drought in the discovery of new drugs.<sup>[1,2]</sup> According to the authors it is expected that new indications could be identified for the existing drugs through the concept of centrifugal pharmacology.

Two technical terms, centripetal that refers to a direction from periphery to the center and centrifugal that refers to a direction from center to the periphery distinguish between the current and the proposed pharmacology. Vast majority of the drugs in regular use execute their action through centripetal pharmacology. The administered drug enforces its action on the living organism and is proportional to the dose administered. Doses of certain powerful drugs such as anticoagulants, ergotamine or quinidine must be carefully controlled to avoid fatal outcomes.<sup>[3,4, 5]</sup> The living organisms have limited resistance against the invasion of the administered drug. The concentrations of drug molecules in the body tissues are responsible for the action under centripetal pharmacology.<sup>[6, 7]</sup> No physician ever wishes for rebound effects, withdrawal symptoms, side effects

or toxic reactions but they keep cropping up in many drugs. A glance through a given drug monograph shows that the listing of side effects is more extensive than the indications.<sup>[8]</sup> The new approach will facilitate making use of this vast resource of side effects to initiate the centrifugal pharmacological actions for therapeutic purposes on the basis of opposing reaction of the body.

A pharmacological monograph of a given medicine is structured in favor of our prejudices. The categories that please us consist of pharmacokinetics, pharmacodynamics (Centripetal pharmacology), indications and the posology. The unpleasant areas consist of contraindications, cautions, side effects, toxic reactions, withdrawal symptoms and interactions.<sup>[9]</sup> The side effects of drugs as viewed currently stand out only because of our bias towards desirable effects and our present inability to make use of them gainfully. In reality, the side effects too are the effects of comprehensive action of a drug. Sometimes it takes over a century to realize that a side effect in fact is a valuable indication. Classic example is the use of acetylsalicylic acid as an anticoagulant.<sup>[10]</sup> There are many other modern drugs such as sildenafil, tolbutamide and chlorothiazide that have been discovered based on their side effects. Side effects will be a rich source of indications under the proposed system.

Reaction under centrifugal pharmacology can take place for long periods even in the absence of any drug molecules in the organism. This is because it is the body that is reacting and not the drug molecules. The living organism is viewed more or less as a physical entity for the convenience in the application of drugs under classical pharmacology. Acidity neutralized with bases, constipation relieved with laxatives, spasms relieved with spasmolytics and scores of such anti-sickness drugs are in use. However, a substantial number of medicinal agents such as vaccines and desensitizing agents in regular use are acting on the basis of the proposed centrifugal pharmacology. Most of these drugs act independent of the dose or quite out of proportion to the administered dose.

The article revolves around four distinct drug activity areas. i) Action under indications of a given drug, ii) its side effects and toxic reactions, iii) the rebound effects and withdrawal reactions providing evidence of opposing bodily reaction and iv) the proposed centrifugal pharmacological action opposing i) and ii) both of which by themselves belong to centripetal pharmacological actions. The actions under iii) and iv) belong to centrifugal pharmacology.

Two other mechanisms central to the study are, i) similarity of the administered drug to the disease and ii) the opposing bodily reaction to the initial drug action. Conditions in which drugs are used within the normal physiological range as in replacement therapy and in correcting physiological disturbances may not be related to the subject under discussion.

The new therapeutic approach proposed here is not suitable for acute life-threatening conditions. Time taken for symptom gathering during consultation and selecting a drug that matches these symptoms are time consuming. The action under the proposed system is liable for greater variation than modern therapy.

### Early medical concepts

To understand the principle of centrifugal pharmacology, it requires the discussion of a variety of therapeutic approaches that remain neglected and out of focus at present. An alternative medical system that functions entirely on centrifugal pharmacology is homeopathy implying that its principles should have wider potential for application in other therapeutic systems as well. The reaction of living organisms that tends to oppose an incoming agent or stimulus whether chemical, medicinal, radiation or emotion is the basis of the new concept. There is a little discussed early classification of pharmacological activity of a drug in relation to natural manifestation of a disease in a patient.<sup>[11]</sup> The classification is based on the relationship of the manifestation of drug action on living organism to that of the disease and whether the relationship is the same, similar, opposing or unrelated.

*Isopathy:* This is based on the axiom “*Equalia Equilibus Curentur*” meaning same cures the same. This is also referred to as Homopathy. Therapeutics based on this system has very little application. Autologous-vaccine is an example.<sup>[12]</sup>

*Antipathy:* This approach is based on the axiom “*Contraria Qontraris Curentur*” meaning opposite cures the opposite. Many modern drugs act on the antipathy basis. Use of laxatives in constipation is an example.<sup>[13]</sup>

*Homeopathy:* The axiom here is “*Similia Similibus Curentur*”. A medicinal agent that has the ability to produce similar symptom picture in a healthy person to that of a disease is able to cure the disease when administered in minute doses. Use of digitalis homeopathic dilutions in heart failure is an example.<sup>[14]</sup> Homeopathic system has made great strides and is said to be the most widely practiced system in the world next to modern medicine (Allopathy). The popularity continues despite scores of misplaced clinical trials indicating that it is only just as effective as placebo.<sup>[15]</sup> Erroneously, in these studies a single homeopathy drug is given to all cases of a given disease under test, in the manner of administering a modern drug.

*Allopathy:* This means the use of a medicine that has heterogeneous or unrelated activity to that of the disease in question. The term allopathy was coined by the founder of the homeopathic system of medicine 200 years back so as to distinguish the two systems.<sup>[16]</sup> Modern medicine is currently referred to as Allopathy. On close examination it can be seen that allopathy makes use of medicines belonging to all these ‘pathies’ described above and therefore it has no grand axiom.

The popular medical sayings such as ‘destroy a poison with a poison’, ‘that which can cause can cure’ and that ‘the likes are cured by the likes’ are phrases that relate to centrifugal pharmacology. The Ardent-Schultz rule comes closest to the modern explanation of the centrifugal pharmacology mechanism.<sup>[17]</sup> It states that “weak stimuli excite physiological activity, moderate stimuli favor it and strong stimuli arrest it”. This rule has been replaced currently with the physiological term ‘hormesis’.<sup>[18,19]</sup> Studies in micro dosing of modern drugs where clinical trials are carried out with 1/100<sup>th</sup> of the regular dose may facilitate the understanding of centrifugal pharmacology.<sup>[20]</sup>

### Drugs are a form of disease forces

Medicines are a form of disease-causing agents and this phenomenon is referred to as iatrogenic diseases. One can easily imagine the prednisolone disease, quinine disease and ergotamine disease. Two conditions associated with prednisolone are referred to as Moon Face and Buffalo Hump.<sup>[21]</sup> The last two agents, quinine and ergotamine have established names for their drug induced diseases, cinchonism and ergotism.<sup>[22,23]</sup> Almost all manifestations of malaria coincide with cinchonism

pointing out the similarities of diseases and drug actions. (Table 1) Strychnine poisoning and tetanus present very similar symptoms so that it is difficult to tell them apart.<sup>[24]</sup> Under cardiac glycosides the British National Formulary says "It can sometimes be difficult to distinguished between toxic effects and clinical deterioration because symptoms of both are similar".<sup>[25]</sup> The common meeting point of both medicines and diseases is that they both have a chemical basis for activity though less obvious in the case of diseases. Although it is generally viewed that the drugs are fighting diseases, in reality one disease is being

countered by another form (drug) of a disease. Often a patient has to terminate the use of a drug when side effects show up in greater intensity than the disease. This in fact is a situation where the drug disease begins to manifest stronger than the disease being treated. Signs and symptoms of a drug disease can be initiated easily by administering a given drug to a healthy person in regular doses for some length of time. A systematic collection of these signs and symptoms will constitute the drug picture on which the indications will be based under centrifugal pharmacology.

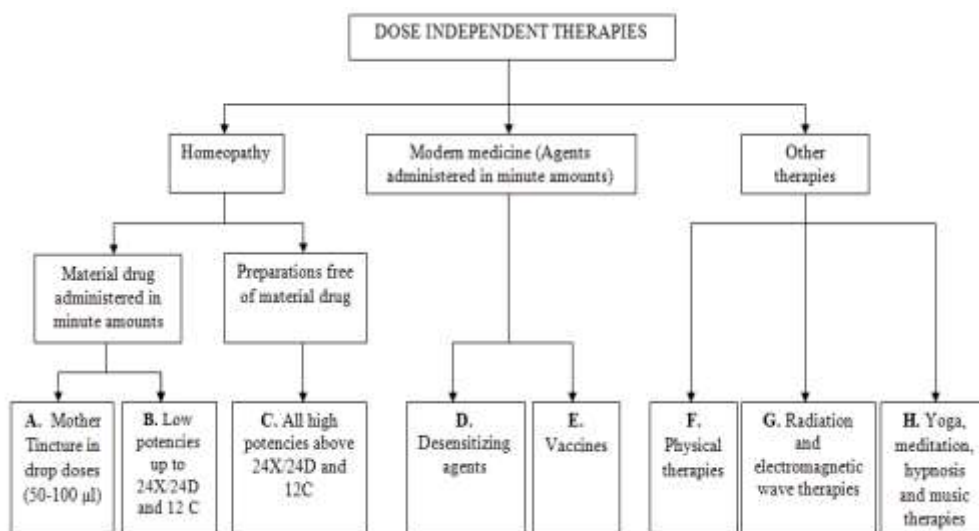
**Table 1: Drugs as a form of disease displayed by comparative symptomatology between malaria and quinine action.**

Signs and symptoms	Malaria	Quinine
A. Subjective	Feverish, muscular pain, fatigue.	Feeling hot, shivering, muscular pain, numbness.
	Headache, nausea.	Headache, dizziness, fainting, imbalance, slurred speech.
B. Signs and symptoms	Periodical shivering, high temperature (38C), drenching sweat.	Chill, fever, sweat, sore mouth, aches.
	Vomiting, diarrhea, dehydration, jaundice.	Vomiting, diarrhea, loss of appetite, jaundice.
	Sudden drop in BP. Acute Respiratory Distress Syndrome.	Allergy, hives, swollen face, lips, wheezing,
	Pulmonary edema.	-
	-	Purple rash, bleeding spots in skin, hemoptysis.
	-	Palpitation, bradycardia, fibrillation, cardiac arrest.
C. Laboratory findings	-	Visual and color vision defects, ringing in ears.
	Destruction of RBC, anemia.	Hematuria, anuria.
D. Complications	Hypoglycemia.	Low blood sugar
	Cerebral malaria, fits, kidney failure, swelling of spleen, pregnancy complications.	Seizures, cinchonism.

Under more serious complications incidental to both the diseases and the drugs, they can cause fetal damage, bone marrow depression, cardiac arrest, complications in special senses and psychological disturbances. They both may follow up with long lasting sequelae.<sup>[26, 27]</sup> Hence both the drugs and the diseases belong to disease causing agents among the living organisms.

#### **Dose Dependent and Dose independent therapeutics**

Broadly speaking, centripetal pharmacology falls under dose dependent therapeutics and centrifugal pharmacology represents dose independent therapeutics. Under dose independent therapies, there are no measurable mass of a drug involved and the cages C, F, G and H in the flow chart are absolutely free of any material drug (Figure 1). Even the motion acting as a stimulus can make a person sick as in motion sickness. Similarly, considering temperature as the stimulus, when the body is exposed to chilly winds, it follows up with a feverish reaction.



**Figure 1: Flow chart indicating dose independent therapies.**

These two dose categories are fundamental in understanding the subject of secondary pharmacology. The popular dose dependent therapies have well established dosing schedules. Under dose independent medication, a single dose of BCG vaccine administered at birth is effective a life time. The vaccine has just a trace of active principle barely visible.<sup>[28]</sup> Even a skin scratch with a trace of the medicinal substance may precipitate shock as during the sensitivity tests. In dose independent therapies, there is no incessant dose repetition, rather the therapies are phased out, weeks, months or years apart as in the case of vaccines. This is because the centrifugal activity carries on in the absence of the drug molecules since it is the biological system that is responsible for these effects.

Studying the basic principles of the homeopathic system of medicine and the basis of homeopathic treatment modalities are most helpful since it operates entirely on dose independent therapeutics. This system is quoted here since it has the most resourceful ready information in understanding the concept of centrifugal pharmacology which is otherwise difficult to access. For the awareness, homeopathy is the only truly European system of medicine as it was developed entirely within Europe- Germany, France and the United Kingdom before spreading to other parts of the world. A section dedicated to homeopathic medicine can be found in the British Pharmacopoeia.<sup>[29]</sup> Established over 200 years ago, currently with an inventory of more than 5000 medicines and practiced in almost all countries is testimony to the effectiveness of dose independent therapeutics as well as centrifugal pharmacology.<sup>[30]</sup>

Familiarization of the following fundamentals of homeopathy will facilitate in the understanding and establishing centrifugal pharmacology based therapeutics. The Organon of Medicine spells out homeopathic principles.<sup>[31,32]</sup> The Homeopathic Materia Medica on drug action (drug pictures) is the equivalent

of modern pharmacology.<sup>[33]</sup> Homeopathic case-taking, the Homeopathic Repertory with cross references of drugs to a given sign or symptom of a disease and the potentizing process in which serial dilution of drugs are carried out coupled with forceful stroking at each dilution step are unique to this system.<sup>[34, 35, 36]</sup>

All said, homeopathy as well as centrifugal pharmacology is only another way of applying drugs in therapeutics everything else in medical science being the same. Scores of clinical trials on homeopathy performed by allopathic medical teams yielding negative results only prove that homeopathy fails when practiced under the principles of a different medical system, allopathy.<sup>[37]</sup> It is unethical to undertake such studies without a subject specialist or the research team members themselves familiarizing with the above spelt out subject areas specific to homeopathy. The daily practiced 200 years old extensive field study on homeopathy with all shades of patients, royalty to common man in their 'Collective Intelligence' is over bearing and prevails over clinical trial studies.

All higher potencies of homeopathic drugs are devoid of material drug and are dose independent. (Figure I) This was the main stumbling block in the wider acceptance of homeopathy. The subatomic particle photon based delayed luminescence analytical procedure of high potencies had been discovered by German and Indian scientists. It was found to yield results that are characteristic of the original material drug and the high potency.<sup>[38]</sup> This study will be the most absorbing reading for those who are looking for the scientific basis of thus far elusive mechanism of action of high potencies.

### Centripetal pharmacology

This is the popular pharmacology, the afferent or the centripetal pharmacology that brings to bear enforced drug action on living organisms. The drug action takes

place from the periphery to the center. The drug gets absorbed from the outer most GIT mucous membrane into the blood stream and diffuses into the extracellular tissue. It reaches the cell surface and penetrates into the cell interior. Inner most sites in the centripetal pathway are the neurons, cells of the retina, islets of Langerhans, conducting tissue of the heart, gonads and osteoblasts. Some drugs find their way into the cell nucleus and to the genetic material.

The periphery to central reach of the drugs in centripetal pathway is both anatomical and histological. Sometimes a drug brings about one class of therapeutic effects at one dose level and another class of therapeutics at another dose level. Some medicines act in locations away from the desired center reminding their similarity to metastasis of diseases. For instance, carbimazole may cause birth defects and inflammation of the pancreas.<sup>[39, 40]</sup>

### Centrifugal pharmacology

Administration of phenobarbitone induces sleep which is the classical action of this medicine. After some days when the therapy is terminated the patient is unable to fall asleep.<sup>[41]</sup> This is the natural body reaction to any stimuli in which the original action is opposed by a bodily counter reaction. Laxatives similarly bring out an opposite reaction where the patient suffers constipation following stoppage of the medicine. Fast acting antacids lead to acid rebound where more acid is secreted by the stomach under this counter acting centrifugal pharmacology.<sup>[42]</sup> Fast-acting antacids such as sodium carbonates were discouraged from use. In order to overcome this, modern antacids are formulated so as to gradually neutralize the acid such that the body is deceived and does not sense the invading drug or the centripetal pharmacological action. As a result, the opposing centrifugal pharmacological action is not initiated. Many drugs are not withdrawn abruptly and instead tailored off in decreasing doses to avoid cropping up of withdrawal symptoms, which belongs to centrifugal pharmacology. A case report of cholinergic rebound syndrome following withdrawal of clozapine had been published.<sup>[43]</sup>

Instances of the same drug causing contradictory effects are well known. Diazepam causes tranquility but it may also cause excitation.<sup>[44]</sup> Out of these contradictory effects, it is possible that one could be identified as belonging to centripetal action and the other to centrifugal action. Certain drugs bring out serious centrifugal pharmacological reactions in case the drugs are stopped abruptly. The hypotensive propranolol brings about high blood pressure together with chest pain, heart attack or even death.<sup>[45]</sup> These reactions can take place in a patient who had no previous heart disease and is a clear indication that they belong to centrifugal pharmacological effects. In Epilepsy, abrupt stoppage of Topiramate leads to increased seizures.<sup>[46]</sup> Stoppage of analgesic opioids lead to generalized pains.<sup>[47,48]</sup>

In the recently introduced Clinical Trial Phase- 0 a drug under investigation is administered to 8-10 healthy human volunteers.<sup>[49]</sup> This presents a good opportunity to study the entire range of unhindered and non-discriminatory effects of a drug. At this stage, there are no typical indications and the drug effects include those that will be later classified as side effects and toxic reactions. They stand to represent the native activity of a drug on human system and express the comprehensive natural drug picture in relation to living organisms.

The totality of the reactive nature of a drug in relation to the living organism is referred to as the 'Drug Picture'. Generally, the unwelcome sections of classical pharmacology monographs contribute to the bulk of the drug picture. The collective drug picture, head to foot has to be documented for the possible centrifugal pharmacological application. Usual diagnosis of the disease apart, in the new therapy the focus must be about the 'diagnosis of the similar drug' by matching the signs and symptoms of the patient with best match drug picture.

### Instances of centrifugal pharmacology in modern therapy

All of the allergens and desensitizing reactions bring about their activity by centrifugal pharmacological mechanisms. There is but a whiff of the responsible agent bringing an enormous out pouring of pharmacological response. Some of these actions are curative while others life threatening.

Capsaicin alkaloid extracted from capsicum is a known irritant causing burning sensation in the mucous membranes and skin. The capsaicin topical formulation 0.025 – 8 % w/w is used as an analgesic and a counter irritant in many conditions such as diabetic neuropathy and hepatitis neuralgia.<sup>[50]</sup> Digitalis had a staggered history (William Withering 1785), once as a useful therapeutic agent for many decades and then as a dangerous cardiac poison. The isolated cardiac glycosides were later established as standard drugs for cardiac failure and now these are sidelined again. This was possibly due to non- realization that its beneficial actions were based on efferent or the centrifugal pharmacology and that the poisonous effects were due to afferent or the centripetal pharmacology. These effects depend on the dose and the manner of its administration. It has anti-arrhythmic properties in micro doses but induces arrhythmias at higher doses.<sup>[51]</sup> The concept of centrifugal pharmacology may succeed in bringing clarity to the digitalis therapy. Ipecacuanha is a GIT irritant causing vomiting but in small doses it improves the appetite.<sup>[52]</sup> Medications such as liquid extracts of belladonna, nux vomica, opium and ipecacuanha in allopathic practice are employed in homeopathy too but using in minute doses for the opposite action.

Cancer vaccines prepared with the tumor associated antigens are being researched for the possible anticancer

activity that represents centrifugal pharmacology.<sup>[53, 54]</sup> It is likely that the off- label use of colchicine in pericarditis exerts its action through centrifugal pharmacology. Many of the colchicine side effects such as pain, discomfort and tightness of chest, cough, breathing difficulty, weakness and effects on heart beats are similar to the symptoms of pericarditis.<sup>[55, 56]</sup> There is the possibility that the drugs such as digitalis in routine use without any clearcut active sites, receptors, enzyme or metabolic pathways may be exerting their action under centrifugal pharmacology.

### Centrifugal pharmacology future prospects

Under the modern drug discovery, Clinical Trials Phase-0 appears to be modeled after the 200 years old principle of 'drug proving' in homeopathy. It is most suitable in establishing centrifugal pharmacology since healthy volunteers are involved. For the purpose of completion of the drug picture, symptoms generated from a number of volunteers of both sexes have to be pooled together.

In any investigation of the centrifugal pharmacological therapeutics of a drug, the dose employed should be an amount just sufficient to trigger an opposing reaction. A small percentage of the standard dose, 10% - 0.01% or smaller may be sufficient. Repetition of the dose should be at longer intervals than the regular frequency. The idea is to stimulate and initiate the bodily centrifugal pharmacological action and to avoid the regular pharmacological action. Response may take a number of days. At present, centrifugal pharmacology based therapeutic interventions may not come handy since a text book with a collection of drug pictures is not available. However, one can figure out the drug picture on the basis of colchicine already described and lansoprazole drug picture described two paragraphs below.

Initial experiments in centrifugal pharmacology therapeutics may be more suitable with chronic diseases and those diseases that progress slowly. The relief will be very gentle with no prospect of any side effects due to small doses involved. The prescriber must refer to case-taking record for the follow up. Under centrifugal pharmacology a completely new set of drugs may be indicated for a given condition. This is because the selection of the drug to match disease symptoms depends on the 'drug picture' of a given drug.

A suggestive summery 'drug picture' of Lansoprazole based on its side effects is given below. This is the basis of centrifugal pharmacological prescribing which is radically different to those of classical indications. Lansoprazole in minute doses will be the drug for disease conditions with following symptoms in a patient. "The patient suffers from giddiness, sleep disturbances, depression and para-esthesia, disturbances in taste, stomatitis, dryness of mouth, glossitis, hepatitis with jaundice, pancreatitis, fever, GIT disturbances, disorganization of blood, pain in joints, wrist, hips and

back. Muscle spasms in hands and feet, tremor, visual disturbances, tinnitus, photosensitivity, itching, peeling off skin, purpura, loss of hair, nephritis with edema".<sup>[57,58]</sup>

### CONCLUSION

The article brings to focus the idea that discoveries of new therapies may be possible outside the increasingly expensive research based on receptor sites. It proposes the new branch of pharmacology by way of efferent, secondary or the centrifugal pharmacology. The unwelcome actions of drugs in current use such as the side effects, rebound effects, withdrawal symptoms or toxic reactions have been identified as areas in which useful secondary pharmacological indications could be identified. The combined information on unwelcome symptoms of a drug exceeds those of the indications by a large margin. Centrifugal pharmacology could be the avenue to do justice to this wealth of information on drug action turning them into useful therapeutics. The new therapy is applicable to all cases of curable diseases. Certain surgical cases such as anal fistula that had demanded repeat surgical interventions have been cured by homeopathy in which the therapeutic mechanism is based on centrifugal pharmacology.

It is proposed to regard drugs as another form of diseases and the therapeutics are viewed as an interplay between two disease forces. It had been reported that there were only two cases of superimposing influenza infections during the current Covid-19 pestilence exceeding 600 million cases. The more powerful Covid-19 disease had held back the weaker influenza infection.

The principles of centrifugal pharmacological therapeutics can be summed up as follows.

- i. The action under centrifugal pharmacology is initiated as a bodily response opposing the incoming drug action under classical (centripetal) pharmacology.
- ii. The action continues to operate in the absence of drug molecules in the body. There is no urgency to maintain a therapeutic plasma concentration.
- iii. The entire spectrum of favorable and unfavorable actions constitutes the overall activity of a drug on a human being, which is its 'drug picture'. This constitutes the therapeutic scope of a given drug under centrifugal pharmacology for any disease which presents similar symptoms to that drug.
- iv. There is no specific drug for a given disease. However, a certain set of drugs may be more frequently indicated to a given disease.
- v. Under secondary pharmacology, a medicine with a 'drug picture' that has most similar presenting signs and symptoms to the patient must be selected for therapy. The basic therapeutic principle is, 'a medicinal agent that has the ability to produce similar symptom picture in a healthy person to that of a disease is able to cure the disease when administered in minute dose'.

- vi. The alternative medical system of Homeopathy operates entirely based on the principle of centrifugal pharmacology and its principles will aid in the understanding of the subject. There is a false idea that homeopathic drugs are mere placebos and has no drug molecules which is true only about high potencies. A good percentage of homeopathic prescriptions are made with low potencies (dilutions) including mother tinctures all of which have substantial concentration of active substances as shown in cages A and B of figure I.<sup>[59, 60]</sup>
- vii. The therapy is subjected to a high degree of biological variation and the treatment has to be highly individualized. Routine dosing schemes popular with classical pharmacology are not applicable. As per definition under item v) above, there is no specific drug for a given disease.

When the standard therapies have been exhausted, it may still be possible to give relief to patients by resorting to secondary pharmacological interventions. Given the novelty of the subject and the biological variations to which it is subjected to, it may be necessary to have centrifugal pharmacology specialists and pharmacists competent in extemporaneously preparing reduced doses.

#### ACKNOWLEDGEMENTS

None.

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