DISCUSSION

1. Aging and genetic aspects in brief:

In the chapter of Introduction, a brief presentation of a number of personalities of long age is given, with an intention that, when a person has a long life, which is healthy and devoid of complications related to aging, obviously this may be associated with retarded Homeostenosis of critical parameters.

Similarly there has been study of centenarians and the genes associated with aging. Heather E. Wheeler and Stuart K.Kim [1] state that “very little is known about the specific genes that affect the rate of aging or human life span”

They have also given the tabulated form of summary of gene association studies in long lived individuals. These studies pertaining to genes like APOE (ε4 allele of Apo lipoprotein E, as done by Corder E. H. et al. [2] and also, by Kervinen K. et al. [3]

Similarly the role of MTP (Microsomal Transfer Protein) as a marker associated with life span is given by Geesaman B.J. et al. [4]

Like wise, many other genetic studies related to APOC3 (Apo lipoprotein C3), by Atzmon G.et al. [5] and IGFIR (Insulin Growth Factor 1 Receptor mutation study by Suh Y.et al. [6],

Longer telomerase length and association with hTERT (Human Telomerase Reverse Transcriptase is shown by Atzmon G. et al. [7]

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Studies related to Asian and European population with longevity and FOXO3A (Forkhead Box 03A) transcription factor are quoted by H.E. Wheeler and S. K. Kim, throwing light on studies related to serum Iron, Vitamin B\textsubscript{6}, Vitamin B\textsubscript{12}, plasma Arachidonic acid, plasma eicosa pentanoic acid, and many other age related trait studies done by study groups like BLSA, FHA, INCHIANTI, SardiNIA having excellent scientific consistency.

It seems that where there are less age related issues of homeostenosis, the longevity is determined by advantageous molecular scenario created by appropriate genetic function.

These authors have also presented association of parameters like BMI and weight in these age related critical traits in research of Framingham Heart Study. Keeping this in mind we also did the anthropometric study of elderly group.

The DNA Microarray characterization has lead to a new approach of analysis called ‘Genomic Convergence’ This according to authors may help better understanding of aging organ or tissues, and genotype of tissue or organ specific aging genes can have predictive values about declining of function. In future there is good hope for predictivity of homeostenosis as what authors say will provide new dimension to age related functional decline.

Heather E. Wheeler and Stuart Kim have given vivid account relating to genetic polymorphism and longevity, stating the role of ε4 allele polymorphism in genetic etiology of cardio-vascular disorders.
Atzmon G. et al. studied centenarians and long telomeres; (this is interesting as most aging individuals die of usually, hematological or cardio- respiratory disorder and cannot reach the centenary age.)

In our study, the selected anthropometric, hematological, cardiac and respiratory parameters of 50 males and 50 females in age range of 60-80 years were examined, and compared with 15(<4:1 ratio) of apparently healthy counterpart participants in the age range of 17-20 years; because in this young age, there is optimum development of these organ system, yet, they do not have age related changes of senility.

As anticipated the values of different variables in case of females were less than values in case of male participants.

2. Aging and Hematologic study:

Alexander Panda et al. [8] have given an account of human immune senescence and while describing this part, author states that this part of aging related innate immune senescence is incompletely understood. They have mentioned role of diverse cells like neutrophils, monocytes and eosinophils as well as basophils in this context.

This indicates to focus on the corpus of information in age related hematologic changes.

The hematological reference or normal values in form of intervals were selected from various source [9, 10, 11] and compared. Although there was nominal difference among them, but by and large, they were near one another. The sources
selected did not mention standardized reference values for elderly group or aging population; and hence the assessed value was compared with the young adult values

Some experts believe that “Iron can react with oxygen species to form free radicals; leading to protein damage accumulates with age.” And mentioned that too little iron causes anemia and too much iron may be toxic. As such, this indicates necessity to undertake hematologic assessment in aging population.

Sunita Wickramsinghe and Geoffrey McCullough [12] have mentioned that, there is reduction in the amount of trebecular bone and haemopoiesis, accompanied by an increase in fat cells but only in sub cortical regions, in addition, other cells normally present in the bone marrow such as lymphocytes, plasma cells, and mast cells may increase in bone marrow of older people.

Chiu Wah Tsang et al. [13] studied hematologic indices in an older population sample to derive the healthy reference values. These authors mention that the reference values for elderly may differ from those of young people. These authors have given 11 series from different authors giving details of commonly employed hematologic parameters. Two of these series are having large population number between 1000-2000 participants, yet many are in range of 100-200 subjects, this sample size may be perhaps suitable for determining reference values, however the sample size of series of Zauber N. and Zauber A. [14] and Jarnigan J. et al.[15] have sample size nearer to our study. All these authors have presented parameters like Hemoglobin value, Hematocrit, Mean Corpuscular Hemoglobin, Mean Corpuscular Volume, Total W.B.C. count, Total Platelet count, and some biochemical relevant tests. In our study, in addition we did differential W.B.C. count, Mean Corpuscular Hemoglobin Concentration, R.D.W. [Red Cell Distribution Width] and Erythrocyte
Sedimentation Rate. [E.S.R.] Chiu Wah Tsang et al. have studied non Indian subjects who differ in many ways like diet, ethnicity, life style etc. and their objective for study is also different yet in general our results are comparable to their findings. In Indian population study of Preeti Jain et al. [16] and Padalia M.S. et al. [17] have close similarity to our findings. A.J. Sinclair, J.E. Morley and Bruno Velas in Pathy’s Principles and Practice of Geriatric Medicine [18] mention that, the cause of low hematologic parameters in aged is by reason that there is decrease in bone marrow reserves in response to high demand. These authors have mentioned 7.0 % prevalence of iron deficiency anemia at 50 years of age, but according to Chaves, Asher, Guralink et al.[19] by 80 years it goes above 30 %[31.4%],however, the idiopathic anemia of aging occurs in 23.0 % of aged population, due to hemopoietic stress. Also, Pennix B. W. Pahor and Cesari M.et al.[20] have stated that it is due to debility and diminished muscular performance and muscle strength, but Ershler W.[21] has focused on cytokines in causation of anemia in aged. It is noteworthy that Zauber N.P. And Zauber A.G. [22] hold that with aging the hemoglobin level does not change significantly.

Joosten E., Pelemans W. and Hiele M.et al. [23] mention that along with a large number having undiagnosed anemia, prevalence rate in chronic disease associated anemia in geriatric population is 35-40 %, Iron deficiency anemia about8-15 % and vitamin B_{12} deficiency anemia is about 5.0 %.

Pathy’s Principles and Practice of Geriatric Medicine [18] have given an elaborate list of causes of age- related anemia. Accordingly, it may be due to life style changes, like, shopping, cooking, feeding, GIT issues, hormonal issues, neuro-endocrinal issues, or alcoholism, lipid phobia, dementia, bereavement, psycho- social
disturbances, malignancy, GIT infections, neurologic issues, effects of medicines, effect of Opioids, role of Ghrelin, Neuropeptides, CCK, GLPYY, Leptins, role of cytokines, and issues of Oraxin A/ B

It is estimated that aging reduces food intake by about 30 % and may cause anemia according to authors of Pathy’s Principles and Practice of Geriatric Medicine thus this account of nutritional anemia in aging population is clinically also impressive for diagnosis or differential diagnosis of etiologic mechanism operating in a particular case.

The above mentioned factors are not the target problems of thesis and are presented only to demonstrate the plurality of etiologic mechanisms related to homeostenosis of hematologic parameters.

When compared with young counterpart, values of Hemoglobin, PCV, and Mean Corpuscular Hemoglobin Indices were less in aged population as shown in graphs and tables; although, all indices were within normal limits of reference values shown, related to the parameter, in general.

In one study, done recently [24] about elderly population of Vadodara city, there was decrease in comparable values in mentioned parameters with increase in MCV. This was not the case in this study; but, instead of the megaloblastic picture, hematological picture suggestive of iron deficiency was seen in this study. This Suggests that there may be pockets of differing presentation types of in aging population in city, and this being study with small size of population cannot provide any conclusion about the type of anemia affirmatively. It was also noted that however, that the values were close to normal limits in most of the cases. The similar studies [16, 17] done elsewhere gave comparable results.
This indicates need to focus on the corpus of information in age related hematologic changes.

**Study of Cardio-vascular homeostenosis in aging population:**

Desler et al. [25] maintain that, “aging has been demonstrated to reduce the fidelity of myocardial mt DNA resulting in reduction of maximal respiratory capacity. Aging therefore further sensitizes the heart to acute and chronic stress, lowering the threshold of damage the heart can endure.”

In this study, the values of SPO2 in male as well as female subjects were within normal limits and as such no abnormality is detected in these findings.

The radial pulse tracings were showing as per expectation, the changes of heart rate variability common in this age groups, the effect of respiration was also as expected, but as shown in photograph, in rare case occasional low volume beats were noted which too were asymptomatic and hence, not critically suggestive of any noteworthy correlation is discussed.

Heart rate, Rhythm changes, the arterial blood pressure changes in SBP, [Systolic Blood Pressure] DBP, [Diastolic Blood Pressure], and the pulse pressure changes are parameters having bearing and important correlation to disorders of Cardio-vascular system in aged; hence the study of HR[Heart Rate], ECG[Electro-Cardio-Gram] (all 12 Leads), and blood pressure assessment were done.

Fleg J. L. and associates, [26] mention that in supine position, at rest, the heart rate in healthy men does not change with aging. Tsuji H. Larson MG, Venditti FJ et al.[27] state that beat to beat fluctuation of HR commonly known as heart rate variability, steadily declines with age also, as quoted by EG Lakatta and Daniel.
Levy[28], reduced heart rate variability is an indicator of cardiac autonomic regulation commonly found in older people and has been linked to increased and fatal outcomes. EG Lakatta et al. in the same article also hold that isolated Atrial Premature Beats (APB) appear on resting ECG in 5% to 10% of subjects older than 60 years and are generally not associated with heart disease.

Increase in prevalence and complexity of both supra ventricular and ventricular arrhythmias whether detected by resting ECG, ambulatory monitoring or exercise testing occurs in otherwise healthy older patients but not in younger persons, also short bursts of PSVT 1%-2% are seen in apparently healthy individual older than 65 years who were rigorously screened to exclude disease, according to EG Lakatta and Daniel Levy. We found only one case of such ventricular rhythm disturbance as ectopic ventricular beat.

By quoting Hiss, (1960), Simonson & Keys,(1952),Simonson,(1961) Best and Taylor[29], have described details of characteristic changes of ECG associated with aging, like P-Q, P-R, Q-T prolongation in ECG of elderly, with decreased voltage changes in P, R, and T waves, and axis changes of P and QRS waves, with aging. Our observations are shown in the graphs and dedicated tables. In our observation, P wave changes were more common as anticipated as well as, only one case (2%) of asymptomatic ectopic bizarre ventricular complex.

JD Pathak [30] has done milestone study [in 1975] in his monograph of Indian elderly where he has shown HR(mean) as 75.9 beats per minute in males and 76 beats per minute in females, which our corresponding findings are as; 86 beats per minute in males and 85 beats per minute in females. Arterial blood pressure in his series was-systolic- 100-204 and diastolic as 60-130 mm of Hg. He has also given
hypertension values derived by different authors of that time, however, many of those values are not in practice today. Whereas in our series systolic blood pressure value was 138 mm Hg in males and 136 mm of Hg in females whereas diastolic in males was 80 and in females was 81 mm of Hg. [by digital B.P. apparatus].

While presenting ECG changes JD PATHAK mentioned that, in his series, 2/3 of participant population had no abnormality and 1/3 had only minor abnormality. Our findings are expressed in tables and graphs related to ECG changes.

He states, occurrence of about 8.3% [15/180] ECG anomalies in his series of participants, where as we found about 10% such anomalies but practically all were of innocent and asymptomatic. He had many extra systole cases [15] and [6] Brady cardia, we had almost all cases of P wave changes and only one case of ventricular bizarre complex.

O P Sharma et al. [31] have mentioned probable occurrence of LVH in over 50% of people, older than 65 years, but in our study [though the sample size is small, we had asymptomatic cases of LVH perhaps, because of exclusion criteria, (where we attempted to exclude such occurrence) and also probably, due to selection of participants had uncomplicated and well gratified daily unaided living with lot of supportive role of their councils and associations, medical health care, adequacy of recreational and physical activities and safer ambience, here in this series, cardiovascular disease is perhaps not as prevalent as 50 % as OP Sharma et al. have observed.

These authors have also presented association of parameters like BMI and weight in these age related critical traits in research of Framingham Heart Study. Keeping this in mind we also did the anthropometric study of elderly group.
Study of Ring and co-workers (1959) as quoted by Best and Taylor, found that blood flow from fingers show a fall from 4.77 to 2.76 ml. per finger volume per minute, between age of 40 and 60 years. Oxygenation at alveolar membrane and response of peripheral blood vessel to heat/ cold is due to change in speed of response rather than final degree of vaso dilatation or vasoconstriction, according to Kety-1956 (Best & Taylor) [29].

SpO2 in our study indicated mild to insignificant change, as it is 97.5[Mean] in males and 97.7 [Mean] in female elderly.

The demonstration of resistance to heart rate variability and higher rise of heart rate with sub maximal exercise as compared to younger group may be due to perhaps impairment in regulatory mechanisms.

Best and Taylor[29] have demonstrated that, work, power, and rate of work of both ventricles diminish significantly with aging, still however, it is also mentioned by quoting work of Burrows and associates, by these authors, that although the tissue succino-oxidase enzyme levels reduce, the isolated intra mitochondrial succinooxidase activity is not decreased.

This may perhaps tempt to hypothesize that the metabolic dysregulation is perhaps less influential than neural or higher central regulation in performance characteristics of ventricular efficiency in aging persons.

According to J.D.Phatak, [30] normal range of heart rate as set by AHA is 50-100 beats per minute.

He observed the mean heart rate as 75.9 in males and 76 beats per minute in females.
In this study, the mean HR in males is 86.02 Beats per minute and females 85.78 Beats per minute which is higher than values demonstrated by Pathak but still in normal limits. This finding may be because of white coat effect. Our findings of elderly group’s blood pressure – Systolic, Diastolic and Mean Blood Pressure is comparable with those of other investigators.

The basal blood pressure as mentioned by Pathak, in 140 old males is 136.9 mm Hg. (Mean) Systolic; and in 40 females (old) is 142.3 mm Hg. (Mean) Systolic; and Diastolic (Mean) blood pressure was respectively 83.9 and 82.7

For the study of ECG, we took the help from book of Tomas Gracia[31], and Leo Schamroth.[32]

Schamroth has mentioned about cardiovascular “Normality and Abnormality” stating that, Electro cardiographic abnormality may occur in normal healthy persons and in absence of organic heart disease; and also, Organic heart disease may occur with normal electrocardiographic patterns.
**Respiratory System Homeostenosis:**

O.P. Sharma [33] while giving changes in elderly, upper respiratory structures, chest wall, Respiratory muscles, lung structure changes like shallow alveoli, increased diameter of alveolar duct and Respiratory Bronchioles described. Decrease of Mean Bronchiolar Diameter, which is the main determinant of air way resistance, is said to decrease significantly and this may be the leading clue to FEV1/FVC changes.

Author of Fishman’s Pulmonary Disease and Disorder [34] has given numerous changes associated with aging in Respiratory System, like tissues of lung, in airways, changes in mechanical properties, surface forces and also changes in macro molecules in aging lung which are useful to understand Respiratory Homeostenosis of aged. Lung parenchyma changes like those in pulmonary alveoli and bronchiolar dilation are described. Increase of Mean Linear Intercept, decrease of surface: alveolar volume ratio, net decrease of 15% in alveolar surface area, diminished recoil pressure at defined lung volume, decreased Gas / Liquid interface and surface area of lung are important age related changes treated in depth by them. Moreover, increase in pleural and pulmonary elastin and d-Aspartic acid with changeover to $^{14}$C.

Murray and Nadal have described many respiratory changes in elderly individuals. [35]

Lowery E.M. et al. [36] have given many salient observations of age associated changes in their article. A.P. Fishman et al [34] have expressed that age related changes in connective tissues *do not* provide sufficient explanation for diminished elastic recoil found in aging.
Also structural molecules like elastin etc. are affected in such a way that there is diminished elastic recoil and diminished pulmonary compliance. Due to trapping of air in the small air ways, diminished elastic recoil, diminished force of strength of diaphragm and other respiratory muscles and thoracic stiffness. R.V. increases; but VC, PEFR, FVC, FEV1, and FEV1/FVC decrease with aging. FRC is mentioned to have increase with aging. DLCO and SaO2 and PaO2 diminish. Air way reactivity is increased and so also FRC and RV. [Our SpO2 value indicates mild to nil degree of depression]. Respiratory drive for hypoxia and hyper carbia is reduced.

Above mentioned changes clearly describe that these changes conjointly play role in producing COPD, ↓VC, ↓FEV1/ FVC and ↓PEFR findings.

These observations clearly support the findings of Respiratory Homeostenosis observed by us particularly the FEV1/ FVC and PEFR are diminished in female elderly, because of perhaps contribution of hormonal and psychosocial factors along with factors described by various experts as given above.

The observations of Christopher Dyer and Carlos A.Vaz Fraga et al. [37] give in depth aspects of mechanisms of respiratory functions and structural alterations and aging.

Also Gulshan Sharma, James Goodwin [38] have given an account of effect of aging on respiratory system physiology and immunology and tabulated presentation of anatomical and physiological changes of respiratory system with aging. As mentioned above, FEV1, FEV1/FVC, PEFR, values diminished in our subjects well correlate with the findings of these authors.
The table and graphs of each individual parameter with min, max, mean standard deviation, \( df \), ‘\( p \)’ value etc. are given along with our findings.

The Computerized Spiro meter can give MVV (Maximum Voluntary Ventilation) and SVC (Slow Vital Capacity) but manufacturers of Spiro meter Software have indicated that these assessments are strenuous workouts and hence we did not determine these parameters for our participants.

SVC is assessment of FEV.2L- FEV - 1.2 L can help diagnosing large airway obstructions. These SVC positive individuals are not selected by exclusion criteria on the ground of their having large airway obstruction. Our subjects, particularly female elderly had a mild degree of COPD which is in accordance to Pathak’s observations wherein he states that, FEV1 of both the sexes is about 70%.

This supports our finding of lower vital capacity and FVC in females due to smaller built and poorer musculature.

We have not attempted to assess Respiratory Efficiency Test like 40 mm Hg. Test etc. due to obvious reason of susceptibility of aged participants particularly females to respiratory strain.

From study by Pathak on Senior Citizens of India where Respiratory Efficiency Test, Maximum Breathing Capacity and Breath Holding Time was also quite low and only 9 % to 13 % could reach the normal young adult level. So these tests are omitted by us as the results are shown to be clearly very low.

The NHLBI / WHO Global Initiative for Chronic Obstructive Lung Disease Workshop summary mentions that “a low peak flow is consistent with COPD but has
poor specificity because it can be caused by other lung diseases and by poor performance.”

Our subjects could perform well with, rather preferred conventional PEFR meter than Computerized Spiro meter. The existence of lung diseases was ruled out at an early stage of clinical examination so our findings of PEFR are by this uncomplicated instrument. However, the instrument we used meets Euro scale standards.

Respiratory changes in aging are well summarized by Gulshan Sharma and James Goodwin [38], as well as by Lowery EL, et al. [39].

In literature 2 different respiratory impairment assessment criteria are prevailing. Like GOLD and LMS.

We have attempted to study respiratory variables by computerized spirometry, the ATS (American Thoracic Society) guidelines and adopted in GOLD criteria, because as CA Vaz Fragaso et al.[35] have mentioned that “Spiro metric reference values for the LMS method are currently unavailable for non-white and those aged >80 years.” by quoting two references.

Our method of assessing Spiro metric values and hence criteria we followed for COPD, in line of Global Initiative method; by which, variable of FVC1/FVC as 73.3. % in male participants and about 68% in female participants as shown in tables are assessed.

According to those norms, Mild or Stage I, is FEV1/FVC< 70 %, but FEV1>=80 % predicted. Accordingly in our cases, of females, 68.8 % FVC1/FVC and FVC>/>= 80% is there, suggesting stage I COPD [mild] in female population, of
aging participants by this criteria. In male participants also at degree of reduction in FEV1/FVC is seen (vide graph).

Quoting Hardie JA, Christopher Dyer [40] has clarified that FVC decline with age occurs later than FEV1 and at slower rate, and hence, “There is natural fall in FVC1/VC from about 75 to 70 % by age of 70 years.” This would incorrectly diagnose such older people as COPD cases.

Also, Harris R.S. and Lawson T. V. [41] have mentioned that “the total expired air and sustained air flow are more important than the peak air flow alone in assessing the effectiveness of cough”, whereas, J.A. Smith et al. [42], have mentioned that “there is a predictable relationship between cough peak flow and number of cough re-acceleration produced within a cough epoch.” As such, we have assessed the expiration function by peak expiratory flow meter. It is well known that the elderly population often has cough clearance issues which in this way make the respiratory assessment meaningful.

**Future Scope and Perspectives in Aging Problems:**

The world has at present a large number of aging individuals; and their problems are varied and many.

Unfortunately the animal models for aging experiments are not successful in providing appropriate answer to issues of human beings as their structure, function, biological behavior, and molecular mechanisms are not exactly parallel to human beings, and hence the research about aging has to be done essentially in human beings only, where the ethical and many problems are inherent, including ethnic, life style issues and issues related to psychosocial and genetic issues. This indicates that the
research in aging is not only a challenging work but also a time consuming and expensive work particularly when it is a longitudinal study, with different unpredictable issues like drop outs, changes in diagnostic and assessment technology etc.

It is observed that India is a country with a very large number of young population, but sooner in coming 25 years changes of senility and decline of physical and mental functions and consequent issues of large number of economic, psycho-social, may complicate the fabric of national progress and arouse newer and multiple challenges. The health service sector, human resource sector and finance sector should venture timely to foresee and exercise adequate measures to handle these issues and its congeners successfully.

From medical point of view, if the research by Animal model is not rewarding lately, attempt have been made to resolve the issues by creating a mathematical physiology model to answer some pertinent queries. Such research papers like in rat cardio-myocyte assessment by mathematical physiology have already been seen in research journals of medical science.