PATTERNS AND FACTORS INFLUENCING ANAEMIA IN CHRONIC RENAL FAILURE

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CERTIFICATE

This is to certify that the dissertation titled **"Patterns and Factors Influencing Anaemia in Chronic Renal Failure"** is the bonafide original work of **Dr.PRITI BHAMA S.** in partial fulfillment of the requirements for M.D.Branch–I (General Medicine) Examination of the Tamilnadu Dr. M.G.R Medical University to be held in MARCH 2009. The Period of study was from January 2008 to August 2008.

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DECLARATION

I, **Dr. PRITI BHAMA S.** hereby solemnly declare that the dissertation titled **"PATTERNS AND FACTORS INFLUENCING ANAEMIA IN CHRONIC RENAL FAILURE"** was done by me at Government Stanley Medical College and hospital during January 2008 – August 2008 under the guidance and supervision of my unit chiefs Prof. A.K.Geetha Devi, M.D., (Formerly Professor of Medicine) and Prof. P. Chitrambalam, M.D., now Professor of Medicine.

The dissertation is submitted to the Tamilnadu Dr.M.G.R. Medical University towards the partial fulfillment of requirement for the award of M.D degree (Branch-1) in General Medicine.

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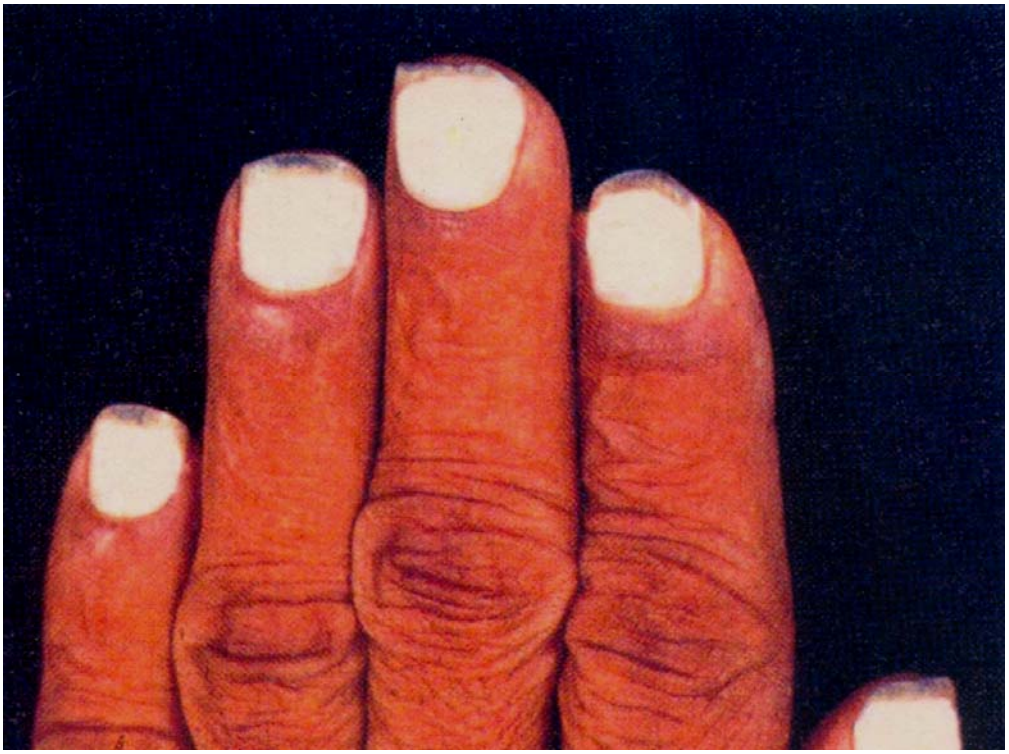
CONTENTS

INTRODUCTION

Fishberg defined uremia in accord with its etymology and original meaning, as a complex of symptoms resulting from failing renal function caused by retention of constituents of normal urine[52]. It is a generalized symptom complex due to a dynamic imbalance between the organism's current metabolism and appropriate renal function. Richard Bright first described the association between anaemia and chronic renal failure. A normocytic normochromic anaemia is present in majority of patients with chronic renal disease, usually observed when glomerular filtration rate falls below 30 ml/min[52].



AIMS OF THE STUDY

PRIMARY OBJECTIVE

Much of the morbidity and mortality in renal failure patients can be attributed to secondary consequences of chronic anaemia[31]. Other factors associated with chronic renal failure may contribute to development of anaemia but erythropoietin deficiency is by far the major factor. Life long replacement therapy with erythropoietin for anaemia correction in chronic renal failure is out of reach for most of our patients who belong to the lower socioeconomic strata. More over many other factors like malnutrition, iron deficiency etc., may be contributing to renal anaemia, correction of which can reduce morbidity due to anaemia considerabley[42]. The purpose of the study is to identify such additional risk factors of anaemia in chronic renal failure.

RATIONALE

By this study, we try to analyze on morphological and distribution patterns of anaemia and its correctable contributing factors if any, so that some benefits can be extended to non affluent renal disease patients also.

STUDY DESIGN

1. Primary objective
2. Secondary objective

To find out morphological and various distributing patterns of anaemia in renal disease.

REVIEW OF LITERATURE

INTRODUCTION

Chronic renal failure is a pathophysiological process with multiple aetiologies resulting in the inexorable attrition of nephron number and function, and frequently leading to end stage renal disease (ESRD). ESRD represents a clinical state or condition in which there has been an irreversible loss of endogenous renal function, of a degree sufficient to render the patient permanently dependant upon renal replacement therapy (Dialysis or Transplantation) in order to avoid life-threatening uremia[52].

The close relationship between haematopoiesis and the kidney has been well recognized for over a century now. Richard Bright in 1835 first described the association between anaemia and chronic renal failure. Subsequent studies confirmed that erythropoiesis is inextricably linked to the kidney through its production of the hormone erythropoietin, the major regulator of red cell production by the erythroid marrow[42]. Thus, any damage to the kidney which includes the cells responsible for the synthesis of erythropoietin and its physiological control, will cause a hypoproliferative anaemia, the severity of which closely parallels the degree of renal impairment. In 1977 human erythropoietin was isolated and purified from urine of patients with aplastic anaemia (MIYAKE et al 1977). This allowed cloning of gene for human erythropoietin (Lin et al 1985) which was then expressed in a suitable

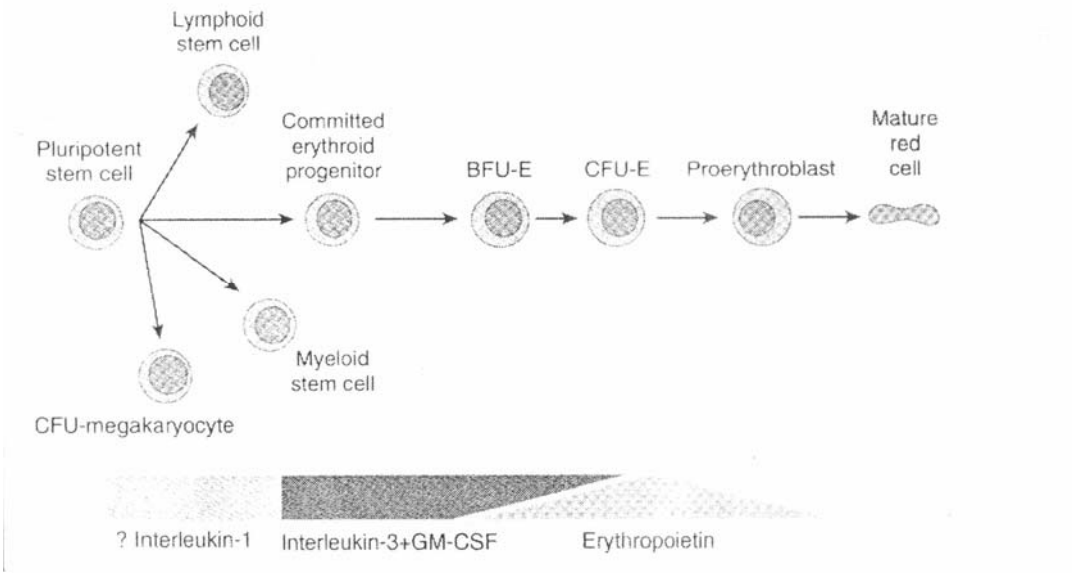
mammalian cell line, making possible for the first time the largest scale synthesis of genetically engineered hormone[47]. Clinical trials in haemodialysis began in Seattle and London towards end of 1985 (Winearls et al 1986; Eschbach et al 1987). It became licensed for use in renal anaemia in 1990. Much of the morbidity and mortality inherent in the renal failure patients can be attributed to the secondary consequences of chronic anaemia. Other factors associated with chronic renal failure may contribute to the development of anaemia but erythropoietin deficiency is by far the major factor.

NORMAL ERYTHROPOIESIS

The erythron is responsible for production of red cell mass of 30 $\pm$ 5 ml/kg in males and 25 $\pm$ 5 ml/kg in females and this is maintained by continual erythropoiesis. Pluripotent stem cells which are capable of both self renewal and differentiation, under appropriate conditions including exposure to interleukin – 1 gives rise to progenitor cells, committed to become myeloid, erythroid, lymphoid or megakaryocytic cells. But differentiation of committed erythroid precursor into primitive erythroid progenitor cell, the 'burst forming unit – erythroid' (BFU – E) is under influence of interleukin – 3 and granulocyte – macrophage colony stimulating factor (GM – MSF). Multiplication and differentiation of the BFU – E and later 'colony forming unit – erythroid' (CFU – E) required the presence of erythropoietin[52]. CFU – E is more sensitive to erythropoietin than BFU – E.

ACTION OF ERYTHROPOIETIN ON RED CELL PROGENITORS

Erythropoietin acts via specific receptors present on early red cell progenitors. There are 500 to 1000 erythropoietin binding cytes per cell. On binding, the receptor – erythropoietin complex internalizes and a variety of cellular response including a rise in intracellular calcium, increases in DNA and RNA synthesis, glucose uptake, globin gene expression, transferring receptor expression and finally haemoglobin synthesis occurs. Also occurs phosphorylation of a defined set of proteins which maintains the cellular viability of erythroid progenitors. This crosses progenitor cells to procede with an endogenous programme of mitosis and terminal differentiation. Erythropoietin also acts on receptors on endothelial cells causing a proliferative response, and stimulate thrombopoiesis possible due to structure homologies between erythropoietin and thrombopoietin, the megakaryocytic growth factor[31].



ADDITIONAL FACTORS REQUIRED FOR NORMAL ERYTHROPOIESIS

The production of approximately 17 ml of red cells each day requires a number of additional factors including iron, folate, vitamin-B_{12}, pyridoxine, ascorbic acid, thyroxine and various trace elements. Of these iron is the most often identified to be deficient in patients both with and without renal failure[31].

IRON ABSORPTION AND METABOLISM

Most of the Iron in circulation is destined for haemoglobin synthesis. It is transported in plasma bound to transferrin, a β – globulin, which binds to 1.3 μg of iron / mg of protein at two binding sites capable of binding two ferric atoms. Transferrin is synthesised in liver and its production is related to the amount of storage iron. Under normal conditions, only 5 to 10% of dietary iron is absorbed, however, absorption can be modified according to iron requirements. Iron that is in excess to cell requirements stimulates the synthesis of ferritin, a soluble protein which is capable of storing iron. Thus, plasma ferritin concentration correlates well with iron stores. Measurements of internal iron exchange are used to evaluate erythropoiesis. The disappearance of transferrin bound Fe from the plasma is used to estimate the plasma iron turn over from which calculation for erythrocyte iron turn over, red cell utilization and marrow transmit time can be derived. Recently more accurate estimate of active erythroid marrow – erythron

transferrin uptake based on plasma iron turn over has been developed. This takes account of the extravascular flux of iron and the ratio of monoferric and differric transferrin, which differ in affinity for cell membrane receptors[43].

Normal haematological values in adults	
Haemoglobin (g/dl) Male Female	 13.5 – 18 11.5 – 16
Haematocrit Male Female	 0.40 – 0.54 0.37 – 0.47
Red cell count (x 10^{12}/1) Male Female	 4.5 – 6.5 3.9 – 5.6
Mean cell volume (MCV) (fl)	81 – 100
Mean cell haemoglobin(pg)	27 – 32
Mean cell haemoglobin concentration (g/dl)	32 – 36
Reticulocyte count (%)	0.8 – 2.0
Absolute reticulocyte count (x 10^9/1)	25 – 100
Total blood volume (ml/kg)	70 $\pm$ 10
Plasma volume (ml/kg)	45 $\pm$ 5
Red cell volume (ml/Kg) Male Female	 30 $\pm$ 5 25 $\pm$ 5
Erythron transferrin uptake (µmol/l.day)	60 $\pm$ 12
Platelet count (x 10^9/l)	150 – 400
White cell count (x 10^9/l)	4.0 – 11.0

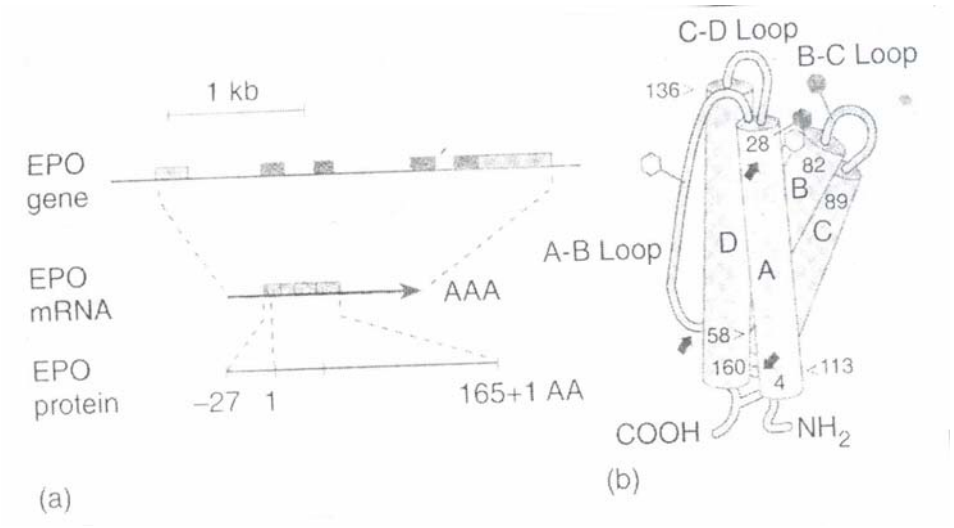
ERYTHROPOIETIN

History: In 1906, French scientists Carnot & Deflandere first suggested the existence of a humoral factor stimulating erythropoiesis. In 1953, Ersley proved that transfusion of plasma from anaemic rabbits produced stimulation of erythropoiesis in recipient animals. Jacobson indicated kidney's role in production of this erythropoietic substance. In 1977, Miyake and co-workers was successful in purifying a few milligrams of this hormone. Amino acids sequence information of this purified material provided the base for cloning of erythropoietin gene and its expression in mammalian cell lines[45].

The kidneys and liver have been unequivocally identified as the predominant sites of erythropoietin production. The controls of erythropoietin production have been identified to be regulated at the level of erythropoietin m-RNA and this regulation occurs predominantly via oxygen dependant control of transcription rate of erythropoietin[39].

THE STRUCTURE OF ERYTHROPOIETIN GENE AND MOLECULE

Gene encoding human erythropoietin is located on chromosome 7 and encompasses about 3000 base pairs. It contains 5 exons and 4 introns and encodes for a 193 amino acid polypeptide. A 27 amino acid sequence at the N terminal part and a carboxy – terminal arginine molecule are cleaved off during secretion leading to 165 amino acid mature protein. Carbohydrate side chains which contributes 1/3 of molecular weight are necessary for both secretion and biological activity of hormone.



(a) Schematic presentation of transcription and translation of Erythropoietin

(b) Three dimensional structure with disulphide bridges and carbothydrate side chains.

MODE AND SITES OF ERYTHROPOIETIN PRODUCTION

Normal serum erythropoietin concentrations in humans are of the order of 10 to 30 mU/ml as determined by radio immuno assays. Assuming a mean serum half life of 5 to 9 hours, endogenous production of hormone, normally amounts to about 2 to 4 units / kg / day.

Erythropoietin concentration alters under a variety of conditions largely reflecting alterations of oxygen delivery to the tissues. Anaemia, caused by bleeding or decreased red cell production is the most powerful stimulus for an increase in serum erythropoietin with an inverse relation between concentration of erythropoietin and haemoglobin concentration. Inhalation of carbon monoxide, an increase in oxygen affinity of haemoglobin, reduction in arterial oxygen tension caused by either cardiopulmonary disorders or decrease in

oxygen tension of atmosphere are all important stimuli for erythropoietin secretion. Hypophysectomy and starvation are associated with decreased concentration whereas stimulation by thyroxine increased concentration of erythropoietin. Thus, conditions of reduced oxygen supply and increased oxygen demand are accompanied by increased circulating erythropoietin concentrations whereas decreased concentration are typical of conditions with increased oxygen supply or reduced oxygen demand[37].

Erythropoietin production has been showed to be primarily regulated by amount of erythropoietin m-RNA in liver and kidneys. Liver is the predominant production site during fetal life whereas kidneys produce most of erythropoietin in adults. In addition, small amounts of erythropoietin m-RNA are found in brain, testis, lung and spleen. Erythropoietin production at these sites could have undefined paracrine effects.

In kidneys erythropoietin is produced in peritubular cells of renal cortex. These are fibroblast like cells which are located in the narrow inter spaces between tubules. Cells in the cortical labyrinth, where convoluted portions of proximal and distal tubules are located and not in the medullary rays take part in erythropoietin production. Even under severe hypoxia less than 20% of cortical fibroblast like cells in this location express erythropoietin and thus it is possible that only a yet unidentified sub group of specialized interstitial cells produces the hormone[15].

OXYGEN SENSOR CONTROLLING ERYTHROPOIETIN PRODUCTION

These mechanisms are the key element in feedback control of erythropoietin production and are sensitive to:

1. Conditions affecting arterial PO_2 and consequently also tissue and venous PO_2 (hypoxic hypoxia)
2. Conditions in which arterial PO_2 is normal and only tissue and venous PO_2 are reduced.

It is unlikely that arterial PO_2 can directly influence erythropoietin production, rather it appears to be tissue oxygen tension that regulates hormone production. With respect to renal erythropoietin production experiments with isolated perfused kidneys showed modulation of erythropoietin m-RNA and erythropoietin secretion in response to alterations of oxygen tension of the perfusate.

It has been showed that exponential increase in erythropoietin production in kidney that occurs with reduction in renal oxygen supply is primarily due to an increase in proportion of peritubular cells that express the erythropoietin gene and single cells respond in almost all – or – none man. This recruitment occurs within cortical labyrinth and is directed from deep to superficial regions. During chronic anaemia signs of morphological damage can be demonstrated in those areas where erythropoietin production occurs. Low oxygen tension in the kidney cortex presumable results from both a restricted delivery of oxygen and high rate of oxygen consumption[34]. The major reason for limited oxygen supply lies in

vascular architecture of the kidney where arteries and veins run in parallel over long distances and close contact between preglomerular arterial and venous beds allows oxygen to diffuse from arteries to veins long before blood reaches peritubular capillaries. So, local tissue oxygen tensions can be much lower than in renal vein. The major determinant of renal oxygen consumption is the transport work of nephron. Since tubular reabsorption is proportional to amount of glomerular filtrate, and the glomerular filtration rate is proportional to renal blood flow, changes in renal blood flow influences both oxygen supply and consumption. It doesn't appears to have much influence in the ratio of both parameters. This explains why kidney is able to adjust erythropoietin production to alterations to blood oxygen content with only a modest confounding influence from changes in renal haemodynamics[35]. So, in renal artery stenosis incidence of erythrocytosis is low. Among different nephron segments that contribute to renal oxygen consumption, the convoluted part of the proximal tubule seems to play an important role in erythropoietin regulation.

CONTROL OF ERYTHROPOIETIN GENE

Accumulation of erythropoietin m-RNA in erythropoietin producing cells results mainly from an increase in transcription rate of gene, but a specific increase in stability of erythropoietin m – RNA may also contribute. Of further importance for hypoxic induction of erythropoietin gene activity is a DNA sequence within the immediate 3' flanking region of the gene[39]. Activation of this enhancer during hypoxia is presumably mediated by a nuclear factor called 'hypoxia inducible factor 1'(HIF 1).

PATHOGENESIS OF ANAEMIA IN CHRONIC RENAL FAILURE

CHARACTERISTICS OF ANAEMIA IN CHRONIC RENAL FAILURE

The peripheral blood film from a uraemic patient usually shows a normochromic normocytic anaemia, occasionally with fragmented red cells or burr cells. The reticulocyte count is usually low for degree of anaemia although white cell count is usually normal[31]. There may be reduced, normal, or increased cellularity of the bone marrow and the erythroid : myeloid ratio may be decreased. But hyperplasia of the erythroid marrow is insufficient to compensate for anaemia present. There is reduced red cell mass but normal total blood volume except in patients who are fluid overloaded. Also a reduction in red cell life span contributes. Factors suggested as contributors to the shortened red cell survival include blood loss, toxic haemolysis and hypersplenism. The depression in erythropoiesis is explained by relative erythropoietin deficiency, the effect of uraemic inhibitors, iron or folate deficiency, aluminum toxicity, and marrow fibrosis resulting from hyperparathyroidism.

IRON KINETIC STUDIES

In chronic renal failure serum iron, transferring, iron binding capacity, saturation and ferritin are usually normal. Ferrokinetic studies in uraemic subjects show that iron – overloaded, transfusion – dependant patients have low erythron iron turnover and red cell iron incorporation, while non-iron loaded patients have near normal erythron iron turn over and a red cell utilization of iron[43].

Ferrokinetics studies in anaemia				
Condition	Haematocrit	Red cell utilization (%)	Plasma iron turnover (mg/dl.day)	Erythron transferring uptake (μmol/l.day)
Normal	42 ± 2	85 ± 4	0.71 ± 0.17	60 ± 12
Haemodialysis transfused	23 ± 3	26 ± 10	0.73 ± 0.16	35 ± 11
Haemodialysis non-transfused	26 ± 5	71 ± 13	0.77 ± 0.18	73 ± 21
Haemolytic anaemia	27 ± 5	72 ± 19	3.86 ± 1.45	400 ± 130

ERYTHROPOIETIN PRODUCTION DURING RENAL DISEASE

END STAGE RENAL DISEASE: Inability of erythropoietin production to respond to the degree of anaemia is independent of causal factors leading to end stage renal disease. It can be due to destruction of erythropoietin producing cells or due to lack of appropriate signals that normally stimulate erythropoietin production[10]. Further evidence indicate that 'the oxygen – dependancy' of erythropoietin formation is maintained in chronic renal failure, but that the system operates at a much a lower level of sensitivity than the intact kidney. A reduction of tubular function contributes to inhibition of normal erythropoietic responds. Also there may be inhibition by immuno modulatory cytokines. Increase in erythropoietin occurs in end stage renal disease as in response to acute blood loss, hypoxia, haemolysis and this possibly originate from extra renal sites.

POLYCYSTIC KIDNEY DISEASE: Anaemia here is generally less severe than usual and occasionally patient may be polycythaemic[2]. Also acquired renal cysts and single cysts may lead to erythrocytosis in haemodialysis patients. Serum erythropoietin concentrations in patients with autosomal dominant polycystic kidney disease are, on average, two fold greater than end stage renal disease of non-cystic origin. In the cyst walls of patients autosomal polycystic kidney disease interstitial cells have been shown to express erythropoietin m – RNA, and cysts derived from proximal, but not those derived from distal tubules where found to contain increased concentrations of bioactive erythropoietin.

RENAL ALLOTRANSPLANTATION: Anaemia of end stage renal disease is usually reversed within three months of renal transplantation. Within hours of transplantation, erythropoietin concentrations increase significantly and after few days plasma concentrations are reached that are, on average, about twice that before renal transplantation[23]. 10 to 17% of recipients develop polycythaemia after successful renal allotransplantation which in some cases appears to be due to inappropriately elevated erythropoietin production and in others due to increased sensitivity of erythroid progenitor cells to erythropoietin, or loss of the feedback control mechanisms.

RENAL ARTERY STENOSIS: Renal erythropoietin production is rather insensitive to changes in renal blood flow. The ratio of oxygen demand to oxygen delivery that governs erythropoietin production, and alterations of renal blood flow will, via a reduction in tubular sodium load, cause concordant changes of both parameters which tend to leave the ratio more or less unaltered.

RENAL TUMOURS: Up to 5% of patients with renal carcinomas have erythrocytosis and 35% of those with tumour – associated erythrocytosis have renal cancer. Accumulation of erythropoietin m–RNA occurs in epithelial tumour cells but not interstitial cells of the tumour stroma.

ERYTHROPOIETIN PRODUCTION AND DRUGS: Acetazolamide reduces hypoxia induced elevations in zero erythropoietin and depending on the dose, this may be due to a decrease in pH which is known to suppress erythropoiesis or due to proximal tubular sodium transport inhibition. Inhibition of erythropoietin is also seen after administration of angiotensin converting enzyme inhibitors.

'URAEMIC INHIBITORS' OF ERYTHROPOIESIS

Substances suggested as inhibitors include polar lipids, arsenic, spermine and spermidine, vitamin A and parathyroid hormone. But to date no inhibitors have been identified and if they exist are of minor importance.

ROLE OF ALUMINUM

Aluminum overload is well know to cause dementia and bone disease which is becoming less common with better purifying of water for preparing dialysate. Severe Aluminum overload in haemodialysis patients is associated with microcytic anaemia which improves when dialysate Aluminum is reduced by deionization of water supply or when aluminum overload is treated with desferrioxamine[40].

IRON AND FOLATE DEFICIENCY

Haemodialysis patients have a small amount of blood loss during each dialysis. In past with kiil dialysers a total yearly blood loss as high as 2.5 ltrs was reported. These days blood loss amounts to between 4 and 20 ml / dialysis with additional loss from frequent blood sampling for haematological and biochemical measurements. With normal iron loss from gastrointestinal tract, in the urine, or during menstruation in addition to loss during haemodialysis, a dialysis patient has a daily iron loss more than 2 mg[43]. Serum iron and transferring concentrations do not give an accurate guide to iron stores in chronic renal patients. Iron stores are best estimated by measurements of serum feritin concentrations, with concentrations less than 80 to 100 micro grams / litre suggesting iron deficiency

Iron reserves (mg) = 400 x [log (ferritin) – log (30)]

Staining of bone marrow for haemosiderin also gives a crude assessment of iron stores.

Folate is readily removed by haemodialysis. So haemodialysis patients may require oral folate supplement. Folate is not removed in significant amounts with peritoneal dialysis and dietary intake alone is usually sufficient. Adequacy of folate stores is best estimated by red cell folate rather than serum folate.

HAEMOLYSIS

The moderately shortened red cell survival in uraemia appears to be related to blood urea concentrations. Severe haemolysis is also associated with over heated dialysate, with several toxins including formaldehyde, copper, nitrates and chloramines. Zinc toxicity also has been shown to cause anaemia[16].

INFLAMMATION

Infections and inflammatory conditions like surgery, pericarditis, vasculitis, malignancy, all reduce response of anaemia in renal failure to recombinant human erythropoietin. Evidences suggest this is mediated by one or more inflammatory cytokines interacting with and inhibiting erythropoietin at cellular level. TNF – α and γ interferon also are implicated.

OTHER HAEMATOLOGICAL EFFECTS ASSOCIATED WITH CHRONIC RENAL FAILURE

LEUCOCYTE ABNORMALITIES

A reduction in capacity of bone marrow to generate granulocytes has been documented in renal failure and there is an enhanced peripheral consumption of neutrophills by the dialyser in haemodialysis patients. Once glomerular filtration falls below 10 ml / minute, the phagocytic activity of leucocytes is impaired. Altered monocyte function with a reduced chemotactic response, reduced phagocytic activity and altered cytokine production occurs in uraemic patients.

Reduced production of IL – 2 by T cells and altered T lymphocyte function occurs in uraemia which is improved by high flux dialysis with poly sulphone membrane. This leucocyte abnormalities contribute to chronic immunodeficiency state characteristic of uraemia.

PLATELET ABNORMALITIES

Defect in megakaryocytic lineage causes platelet abnormalities causing haemostatic problems characterized by prolonged bleeding type. This appears to be due to a defect in activation of the glycoprotein adhesion receptors causing both impaired platelet aggregation and adhesion to the endothelium. The mean platelet life span is reduced in uraemic patients. This is corrected to normal after no less than 12 months treatment with regular haemodialysis. The platelet membrane is affected by increased activity of oxygen free radicals in chronic renal failure and this is corrected by vitamin E. The functional platelet defect of uraemia is reversed by a desmopressin or conjugated oestrogens intravenously possibly by release of Von Willebrand factor multimers from storage sites to plasms. Oestrogen may also act by inhibiting vascular prostacyclins[19].

CLINICAL ASPECTS

PREVALENCE OF ANAEMIA IN CHRONIC RENAL FAILURE

The majority of patients with chronic renal failure develop anaemia and this progressively increases in intensity as renal function deteriorate such that of patients starting dialysis only 3% have normal haematocrit. There is improvement after institution of dialysis, although up to 10% of patients become

blood transfusion dependant and many prior to advent of erythropoietin therapy required intermittent transfusion. Haemodialysis patients tend to have an increase prevalence of severe anaemia than continuous amulatory peritoneal dialysis. This is due to a greater degree of blood loss or haemolysis in haemodialysis patients, and better removal of erythropoietic inhibitory 'middle molecules' in CAPD patients. The severity of anaemia in dialysis patients is independent of etiology of end stage renal disease with exception of patients with adult polycystic kidney disease who tend to have greater haemoglobin concentration[26].

PHYSIOLOGICAL CONSEQUENCES

Various physiological adaptations occur in an attempt to compensate for suboptimal oxygen delivery and these includes modulation of affinity of haemoglobin for oxygen, an increase in cardiac output, and redistribution of blood flow. Symptoms and signs of anaemia include tiredness, lethargy, muscle fatigue, breathlessness at rest or exertion, angina, palpitations, increased sensitivity to cold, loss of appetite, loss of libido, menstrual irregularity, pallor, tachycardia, poor memory and concentration and impaired cognitive and neurophysiological function[33].

BLEEDING DIATHESIS

Chronic renal failure is associated with a bleeding tendency characterized by prolonged bleeding time. Although uraemia results in various abnormalities of clotting factors and platelet function, the level of haematocrit is of considerable importance. Correction of anaemia usually results in return of

bleeding time to normal. This effect is seen both with transfusion and erythropoietin therapy. The mechanism involved is poorly understood, but greater interaction of platelets with vessel wall, enhanced ADP production and improved platelet function may all play a role.

CARDIOVASCULAR EFFECTS

Various adaptive cardiovascular mechanisms to compensate for reduced tissue oxygen delivery from anaemia occurs in chronic renal failure. These include an increase in cardiac output, hypoxia induced peripheral vasodilation and compensatory increase in left ventricular mass causing ventricular hypertrophy. This latter effect, along with concomitant coronary artery disease present in many renal patients, and the reduced oxygen carrying capacity of anemic blood, results in high incidence of myocardial ischemia and symptoms of angina[36]. Other cardiovascular effects include an increase in left ventricular end diastolic dimensions, impaired myocardial contractility, and both systolic and diastolic dysfunctions. As a result, exercise capacity of patients with chronic renal failure is severly impaired, as are measures of respiratory physiology such as maximum oxygen consumption, anaerobic threshold and diffusion capacity of the lungs. Many of these effects are reversed by correction of anaemia with transfusion erythropoietin therapy or renal transplantation.

IMPACT OF HAEMATOCRIT ON MORBIDITY AND MORTALITY

Recent large epidemiological studies have shown that mortality and morbidity are reduced when the hematocrit level is in the range of 33 to 36% and the National Kidney Foundations Dialysis Outcomes Quality Initiative

(NKFDOQI) recommends this target[42]. The recent mortality studies show that hematocrit less that 30% are associated with an 18 to 40% increased associated risk of death and hospitalization compared with patients with hematocrits of 30% to less than 33%. Patients with sustained hematocrits of 33% to 36% over one year appear to have the best outcome compared with patients with less hematocrits.

MANAGEMENT OF ANAEMIA

ASSESSMENT OF KIDNEY FUNCTION

Although GFR is considered the most accurate measure of renal function, it is difficult to measure in clinical practice because it requires a radioisotope and a precisely timed urine collection. Creatinine clearance measurements with timed urine collections provide a reasonable estimate of GFR.

Clinicians most commonly use SCr concentration as an indicator of level of kidney function. However, SCr is affected by factors other than GFR, such as age, gender, race, muscle mass, nutrition and meat intake. With progressive loss of kidney function, there is often reduced creatinine generation related to loss of muscle mass, malnutrition, and restricted meat intake, and the increased tubular secretion and extra-renal excretion of creatinine with advancing renal dysfunction[46]. Consequently, SCr levels and CrCl can underestimate the severity of kidney dysfunction. In this situation, the average of the creatinine and blood urea nitrogen (BUN) clearances with a 24-hour collection more closely approximates GFR.

Cockroft – Gault equation makes out creatinine clearance from serum cratinine values.

CrCl (in mL/min) = 140 – age) x ideal body weight in kilograms / SCr in mg/dL x 72 (multiply by 0.85 for women)

African-American study of Kidney Disease and Hypertension and the Modification of Diet in Renal Disease (MDRD) study equation is as follows:

GFR (in mL/min/1.73 m^2 = 170 x [serum creatinine (mg/dL)] $^{-999}$ x [age (years)] $^{-176}$ x [0.762 if female] x [1.180 if black] x [blood urea nitrogen (mg/dL)] $^{-170}$ x [albumin (g/dL)] $^{+318}$

ASSESSMENT OF ANAEMIA

The NKF published recommendations in 1997, which were updated in 2000, for the management of anaemia among patients with CKD and ESRD. The NKF has recently proposed guidelines for the evaluation of anaemia among patients with CKD[10]. The guidelines for evaluation recommend that patients with a GFR of < 60 mL/min/1.73m^2 should be screened for the presence of anaemia by obtaining a HCT and Hgb. A complete anaemia work-up should be initiated if the HCT is <33% or the Hgb is <11 g/dL in premenopausal females and prepubertal patients or if the HCT is <37% or the Hgb is <12 g/dL in postmenopausal females and adult males. Evaluation of anaemia should consist of measurements of at least the tests listed in Table prior to the initiation of r-HuEPO therapy.

EVALUATION OF ANAEMIA AMONG PATIENTS WITH CKD
Complete blood count with red blood cell indices
Reticulocyte count
Iron studies
Serum iron
Total iron binding capacity (TIBC)
Percent transferrin saturation (serum iron x 100/TIBC)
Serum ferritin
Occult blood in stool

OTHER CAUSES OF ANAEMIA

The possibility of other causes of anaemia among CKD patients must also be considered. It is particularly important to search for nutritional deficiencies among elderly patients, as the prevalence of iron, vitamin B_{12}, or folate deficiency is higher compared with younger individuals[43]. In addition, deficiencies in L-carnitine, vitamin B_6, ascorbic acid and vitamin D may contribute to anaemia. Supplementation with L-carnitine in hemodialysis patients appears to improve the response to r-HuEPO, reduce erythrocyte fragility among hemodialysis patients, and decrease r-HuEPO requirements among patients with CKD. However, supplementation with vitamins C, D, $B_{6,}$ B_{12} and folate is considered of potential benefit in the hemodialysis population. In patients who are diagnosed as being iron-deficient, iron stores should be

monitored every 1 to 3 months to assess adequacy of treatment. This is especially important in the patient being treated with r-HuEPO who is not receiving IV iron[46].

POTENTIAL CONTRIBUTORS TO ANAEMIA IN PATIENTS WITH CHRONIC KIDNEY DISEASE
Nutritional deficiencies
Iron
Vitamins (vitamin C, D, B_6, B_{12} and folate)
L-Carnitine
Chronic inflammation or infections
Secondary hyperparathyroidism
Aluminum bone disease
Chronic blood loss or hemolysis (hemoglobinopathy)
Bone marrow suppression by medications
Bone marrow malignancy
Angiotensin converting enzyme (ACE) inhibitors
Advancing kidney failure with accumulation of toxins normally cleared by Kindneys

The impact of factors related to CKD, or factors that may develop with advancing uremia, must also be considered in both the initial and ongoing evaluation of anaemia. These include the cause of the CKD, use of angiotensin-converting enzyme (ACE) inhibitors and secondary hyperparathyroidism. Once treatment has begun, inflammatory conditions and chronic infections may result in r-HuEPO resistance.

The use of ACE inhibitors is well known to result in anaemia and can also result in increased r-HuEPO dose requirements. Thus, among patients with advanced CKD, in whom there is no longer a significant role for ACE inhibitors to delay progression to ESRD, discontinuation of ACE inhibitors should be considered if there is no other pressing indication for use.

Secondary hyperparathyroidism may lead to bone marrow fibrosis and to reduced response to r-HuEPO, and thus must be considered even among patients with a fairly modest degree of renal dyusfunction[50]. Although uncommon in earlier phases of CKD, aluminum bone toxicity can occur among patients taking aluminum-containing antacids, and this possibility should also be expolored. Finally, advancing uremia may result in worsening anaemia and increasing r-HuEPO requirements and may signal the need to consider dialysis or transplantation.

OPTIMAL TARGET HAEMOGLOBIN

Ideally target haemoglobin should be individualized. An opinion poll of European nephrologists and NKF – DOQI guidelines currently recommend a target haemoglobin of 11 to 12 gm/dl.

The rationales for these target levels are:

1. The level of 33% is just below the lower limit of normal for premenopausal females, and 36% is just below the lower limit of normal for males and postmenopausal females.
2. Worse outcomes have been reported when the HCT is below 30% to 33% (with Hgb 10 – 11 g/dL).

3. Improvement of HCT results in improvement in LVH.
4. Patients function better with higher HCT levels.

HAEMATINIC SUPPLEMENTS

Patients with chronic renal failure are prone to develop a haematinic deficiency state as a result of dietary restrictions, poor appetite and increased blood loss. Such patients are screened for iron, vitamin B_{12} and folate deficiencies and supplements are given as required.

Iron deficiency anaemia can develop relatively early in the course of chronic renal failure[43]. The clinical practice guidelines for the treatment of anaemia in chronic renal failure, established in the United States by the National Kidney Foundation-Dialysis Outcomes Quality Initiative and in Canada by the Canadian Society of Nephrology, recommend the use of intravenous (IV) iron therapy for iron supplementation in hemodialysis patients, most patients on peritoneal dialysis, and some predialysis patients once the patient's serum ferritin falls below 100 ng/mL or transferring saturation below 20%. Furthermore, effective iron replacement and maintenance play a vital role in efficient use of recombinant erythropoietin.

For hemodialysis patients, IV iron has proven convenient and such patients may require supplementation with parenteral iron in excess of 1000 mg to achieve optimal response in hemoglobin/hematocrit (Hgb/Hct) levels. With regard to oral iron, patient compliance has been hindered by patient discomfort when taking such medication. However, patients on peritoneal dialysis and those with chronic kidney disease remain good candidates for oral iron because of

convenience. Some authors doubt the effectiveness of oral iron replancement, as absorption may be reduced in the uremic state especially in those patients taking concomitant phosphate binders. The proof is in the pudding, however, and therefore response to iron therapy should be monitored regularly. If the ferritin and transferring saturation does not improve to the recommended level, then supplement intravenous iron should be used[1].

DOSE AND ROUTES OF IRON ADMINISTRATION

There are multiple possible dosing regimens for parenteral iron, which have been shown to be safe and effective in patients with CKD. Doses studied have included 200 mg infusions monthly for 5 months and total dose infusions of up to 1600 mg.

DIALYSIS

An improvement in anaemia is seen some patients during the first few months after starting dialysis and this may be related to the intensity of dialysis treatment and to an enhanced red cell survival[5]. The improvement in haemoglobin concentration is greater with CAPD than with haemodialysis initially, but three years of treatment, there is little difference between the two modalities. Plasma erythropoietin concentrations are decreased or unchanged during initiation of dialysis suggesting that other mechanisms may be involved.

ANDROGEN THERAPY

Androgens increase erythropoiesis by stimulating endogenous erythropoietin production. They are beneficial only in mild cases under limited by high insulin of side effects such as virilization, muscle and liver damage and cholestasis[49].

BLOOD TRANSFUSION

Before advent of erythropoietin many chronic renal failure patients required repeated blood transfusions to avoid complications of severe anaemia. This has several disadvantages like:

1. Suppression of residual endogenous erythropoietin production and hence erythron activity.

2. Iron overload and tissue iron accumulation.

3. Risk of infections from blood borne viruses like hepatitis B & C, CMV, HIV.

4. Transfusion exposes patient to a wide range of HLA antigens, resulting in cytotoxic antibody production which renders successful renal transplantation less likely by reducing the chance of obtaining a negative cross match[52].

ERYTHROPOIETIN THERAPY

Although the aetiology of renal anaemia is multifactorial, by far the major factor is a relative deficiency of erythropoietin produced by diseased kidneys. Thus, circulating concentration of the hormones is always inappropriately low for the degree of anaemia[45]. Recombinant human erythropoietin was licensed for human use in 1990 which is one of the greatest advances in clinical nephrology in recent years.

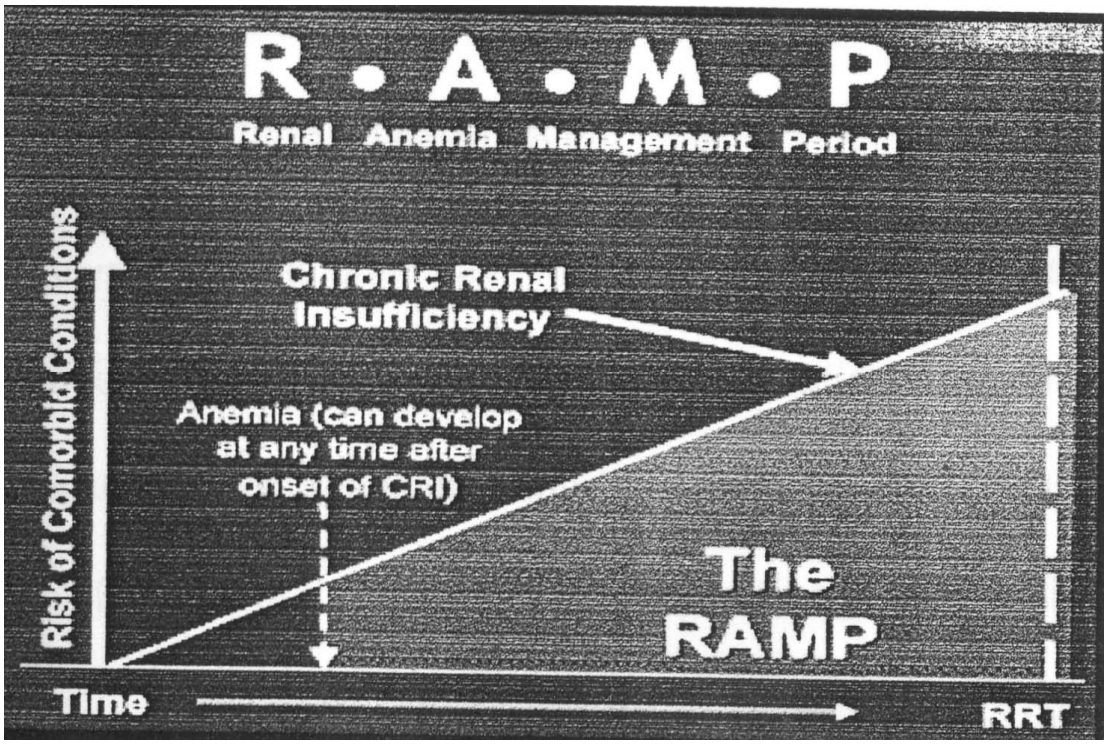
PHARMACOKINETICS

Recombinant human erythropoietin is inactivated by acid in stomach and therefore needs to be given parenterally. The early trials in haemodialysis patients used intravenous erythropoietin administered thrice weekly. Since then intraperitoneal, subcutaneous, intradermal routes of administration have been investigated (Boelaert et al 1989; Macdougall et al 1989). After intravenous administration serum erythropoietin concentrations decay monoexponentially, with elimination half life of 4 to 11 hours (Macdougall et al 1991). Some trials found that half life is shortened with repeated administrations. With intraperitoneal administration peak concentrations are 2 to 5% of intravenous dose and bioavailability is low at 3 to 8%.

With subcutaneous administration peak serum concentrations of about 4 to 10% of an equivalent intravenous dose are obtained at 12 hours, and thereafter they decay slowly such that concentration greater than baseline are still present at 4 days. The bioavailability of subcutaneous erythropoietin is about 7 times of intraperitoneal administration[47].

THE RENAL ANAEMIA MANAGEMENT PERIOD (RAMP)

The high prevalence of anaemia and the historically infrequent use of r-HuEPO for its treatment prior to ESRD, despite the increasing recognition of the association of anaemia with outcomes among patients on dialysis, leads to the realization that anaemia is underrecognized and undertreated among patients with CKD. The concept of a "renal anaemia management period" or "RAMP" was developed to highlight the period of progressive loss of kidney function during which anaemia and other complications of kidney disease develop. During this period, which begins with the establishment of progressive loss of kidney function and varies in duration based on rate of loss of kidney functionand other comorbid conditions, there is an opportunity to intervene with specific measures to control anaemia and the other expected complications of CKD[14]. Treatment of anaemia and other complications should lead to decreasing the impact of associated comorbid conditions. Conversely, failure to treat anaemia and other complications may lead to more adverse outcomes. The operative word in the term RAMP is 'management'. This refers to proactive intervention to control very treatable conditions.



HAEMATOLOGICAL EFFECTS

Approximately 90 to 95% dialysis patients treated with erythropoietin respond with an improvement in their anaemia. On regular therapy an increase in reticulocyte count of 2 to 3 times the baseline is evident at week 1 and increase in haemoglobin concentration is seen at 3 weeks. The optimum target haemoglobin is around 10 to 12 gram / dl after 4 to 6 months of therapy. There is usually a decline in serum ferritin and serum transferrin saturation following commencement of erythropoietin therapy[43]. Radio isotopic blood volume studies show an increase in red cell mass and compensatory reduction in plasma volume such that whole blood volume remains unchanged. Ferrokinetic studies indicate two-fold increase in marrow erythropoietic activity. There is no change in mean red cell life span.

FACTORS AFFECTING RESPONSE TOERYTHROPOIETIN

Patients with more severe anaemia at onset of treatment generally require greater doses. Functional iron deficiency has become increasingly apparent in patients on erythropoietin therapy. Many individuals who are iron replete at start of treatment become deficient under influence of erythropoietin and require intensive iron supplementation[39].

Dialysis patients often have increased occult gastrointestinal blood loss, partly due to greater prevalence of gastritis, peptic ulceration and partly due to increased bleeding tendency due to uraemic platelet dysfunction and heparin administration during dialysis. Presence of acute of chronic infection, inflammatory disease or malignancy frequently causes marked inhibition of response to erythropoietin.

SECONDARY EFFECTS OF ERYTHROPOIETIN

In view of the high cardiovascular mortality among ESRD patients, the prognostic significance of LVH in ESRD, the relationship between LVH and advancing CKD, the role of anaemia in the development of LVH, and evidence that correction of anaemia results in regression of LVH, it would appear that early correction of anaemia with r-HuEPO would result in improved long-term clinical outcomes[36]. Although there are no controlled clinical studies among patients with CKD to confirm this hypothesis, 2 lines of indirect evidence support

the premise that correction of anaemia of CKD with r-HuEPO could result in decreased cardiovascular morbidity and mortality. First, it has been shown that treatment that reduces LVH reduces mortality among patients with essential hypertension. Second, studies in ESRD patients have shown an association between higher HCT and hemoglobin (Hgb) levels and a reduced risk of hospitalization and mortality. Consequently, available evidence supports early treatment of anaemia among CKD patients.

Noncardiac benefits of treatment of anaemia of CKD have also been demonstrated. Revicki and coworkers found that patients in the group targeted to achieve HCT levels > 36% (achieved by 79% of subjects) had significantly improved QOL compared with untreated controls whose mean HCT was 26%. In addition, the United States Recombinant Human Erythropoietin Predialysis Study documented improved QOL as HCT levels increased about 30%.

Cardiovascular System

Longstanding anaemia has profound effects on cardiovascular system many of which are reverse or improved during erythropoietin therapy. There occurs normalization of cardiac output, reversal of vasodilation, increase in mean arterial pressure, improvement in oxygen delivery to myocardium and reduction in ventricular mass. The latter is important as ventricular hypertrophy is an independent determinant of survival in dialysis patients (Silberberg et al 1989)[36].

Cardiovascular effects of erythropoietin therapy
Increased exercise tolerance
Normalization of elevated cardiac output
Increased peripheral vascular resistance
Increased blood pressure (30 per cent of patients)
Decreased symptoms of angina
Reduction in myocardial ischaemia
Reduction in left ventricular hypertrophy
Reduction in left ventricular internal dimensions
Decreased cardiac size on chest radiograph

Non cardiovascular effects

Studies on coagulation and haemostatic pathways shows improvement of aggregation and adhesion of platelets. A prothrombotic state may develop due to increased blood viscocity, reduced protein C and protein S levels, increased thrombin – antithrombin levels and PAI – 1 production.

Erythropoietin induced increase in red cell mass increased haematocrit and blood viscocity[21]. Patients report subjective improvement in memory concentration and other cerebral functions following erythropoietin therapy. Electrophysiological studies shows an increase in amplitude of P3 component of brain event – related potential and a higher score in various neuropsychological tests. Levels of cytotoxic antibodies decline following erythropoietin therapy and phagocytic function of neutrophils improve. Nutritional status of patients treated with erythropoietin also improves.

Non-cardiovascular effects of erythropoietin therapy
Improved quality of life
Improved brain/congnitive function
Decreased uraemic bleeding tendency
Improved platelet function
Improved sexual function
Improved endocrine function
Enhanced immune function
Decreased uraemic pruritus

ADVERSE EFFECTS

Hypertension is the most common and troublesome occurring approximately in 20 to 30% of those patients treated. The risk increases with previous history of hypertension, the rate of increase of haematocrit or target haemoglobin achieved.

Adverse effects of erythropoietin therapy
Hypertension
Seizures / encephalopathy
Vascular access thrombosis
Clotting of dialysis lines
Hyperkalaemia
Myalgia / Influenza like symptoms
Skin irritation

In most instances, blood pressure is easily controlled by fluid removal and use of standard antihypertensives[20].

Several studies in humans have shown no significant acceleration of progression of kidney disease by correction of anaemia with r-HuEPO, provided that blood pressure control is adequate.

Factors inhibiting response to erythropoietin therapy	
Major	Minor
Iron deficiency	Hyperparathyroidism (with marrow fibrosis)
Blood loss	Aluminum toxicity
Infection/Inflammation	Vitamin B_{12}/folate deficiency
	Haemolysis
	Marrow disorders
	Haemoglobinopathies
	Underdialysis
	Carnitine deficiency
	ACE-inhibitors
	? Erythropoietin antibodies

NOVEL ERYTHROPOIESIS STIMULATING PROTEIN (NESP)

NESP is a hyperglycosylated analogue of recombinant human erythropoietin which stimulates erythropoiesis in an identical manner to r-HuEPO. But it has an increased sialic acid-containing carbohydrate content,

making it biochemically distinct from r-HuEPO[34]. An increased amount of sialic acid-containing carbohydrate has been associated with increased serum half life and greater invivo biological activity. So its terminal half life after IV administration is 3 fold longer than for IV rHuEPO. This allows injection for both IV and subcutaneous NSEP to be given less frequently i.e., once weekly or even once every other week. The optimum starting dose is 0.45 microgram/kg once weekly.

MATERIALS AND METHODS

SELECTION AND ENROLEMENT OF CASES

1. INCLUSION CRITERIA

a. All patients should be diagnosed cases of chronic renal disease with anaemia.

b. None of the patients should have received erythropoietin therapy

c. Patients should not be having other significant systemic involvement other than due to uraemia

2. EXCLUSION CRITERIA

Patients having any contraindications as per inclusion criteria shall be excluded from the study.

3. DATA COLLECTION

Simple proforma containing details of patients will be filled up. The following biochemical parameters were assessed as follows:

Haemoglobin: cyanmeth method

Serum creatinine: alkaline picrate method

Feritin: antiferritin labeled with lodine 125

TIBC: Incubating with serum ferric ammonium citrate

Protein: Biuret method

Albumin: using bromocresol green

Cholesterol: Enzymatic colourimetric test

Alkaline phosphatase: p-nitro phenol phosphate

Cholesterol: Enzymatic colourimetric test

Alkaline phosphatase: p-nitro phenol phosphate

Phosphorous: Molydate u.v. method

Stoll occult blood: Guaic test

Uric acid: Spectrophotometric uricase/peroxidase

4. STUDY DESIGN

This will be a cross-sectional study of patients with chronic renal disease and anaemia chosen from Department of Nephrology based on the criteria from January 2008 to August 2008. We propose to study 50 cases of hospital admission for minor ailment (e.g. viral fever) as controls.

STATISTICAL CONSIDERATIONS

The collected data will be statistically analysed. The end point of the study will be completion of analysis of the data.

CORROBORATING DEPARTMENT

1. Department of Medicine, Stanley Medical College, Chennai
2. Department of Nephrology, Stanley Medical College, Chennai
3. Department of Community Medicine, Stanley Medical College, Chennai
4. Department of Biochemistry, Stanley Medical College, Chennai
5. Department of Pathology, Stanley Medical College, Chennai

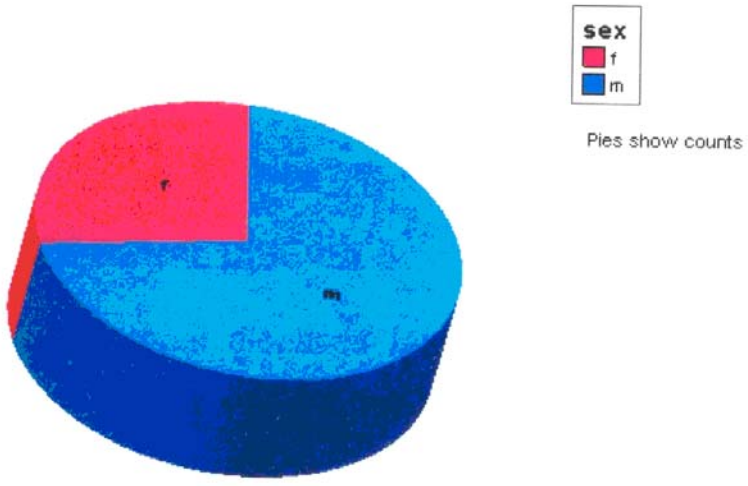
OBSERVATIONS

SAMPLE SIZE

50 cases of chronic renal disease were studied. The observations made in the study were as follows.

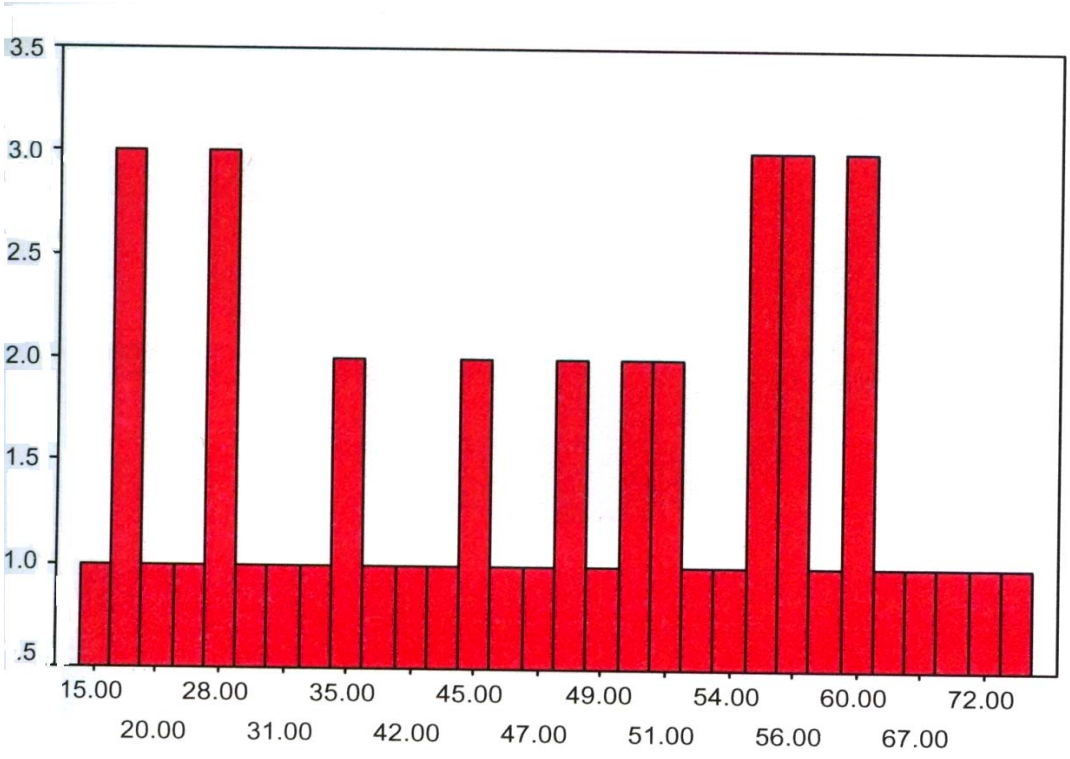
SEX DISTRIBUTION

Out of 50 patients, 14 were females and the remaining 36 males.



AGE DISTRIBUTION

Age distribution ranged from 15 years to 77 years. The variation is from 15 to 77 years in males and from 16 to 56 years in females.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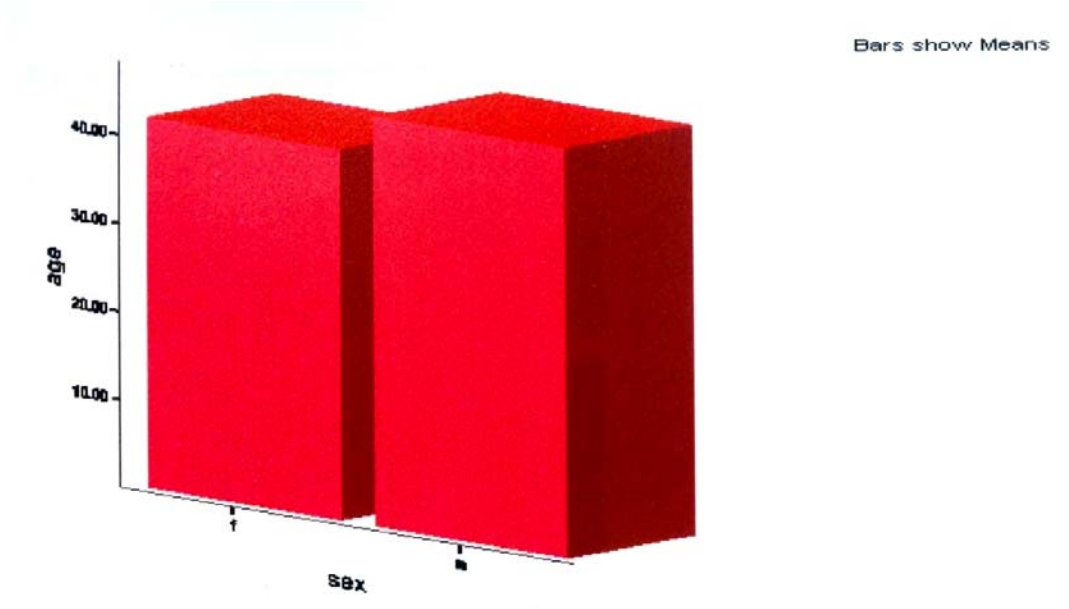
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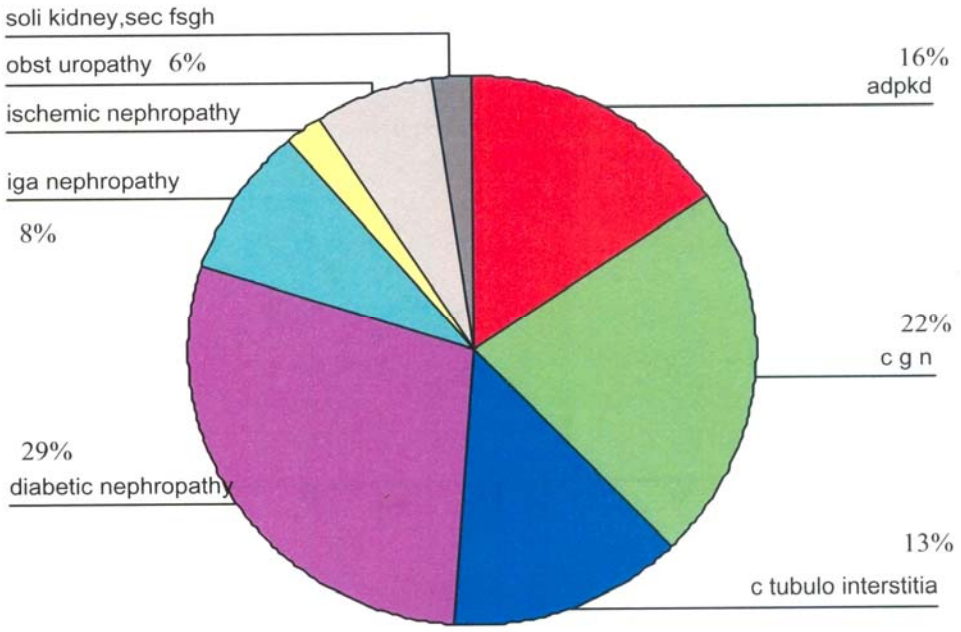
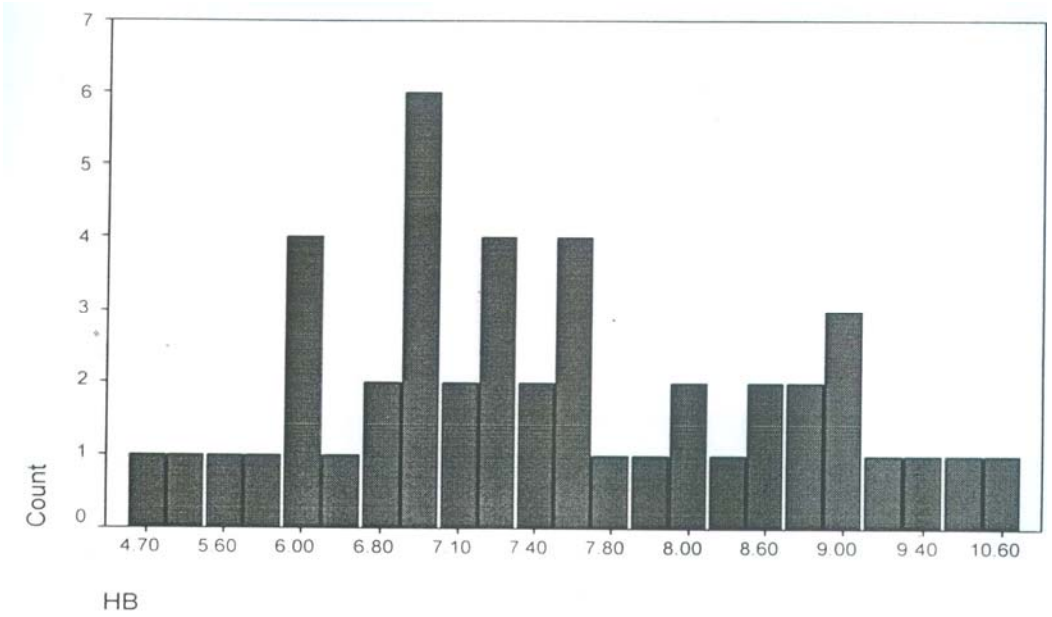
Mean age of females was 41 and that of males was 47.

NATURE OF RENAL DISEASES

Intrinsic renal diseases leading to renal failure were numerous of which diabetic nephropathy was the most common.

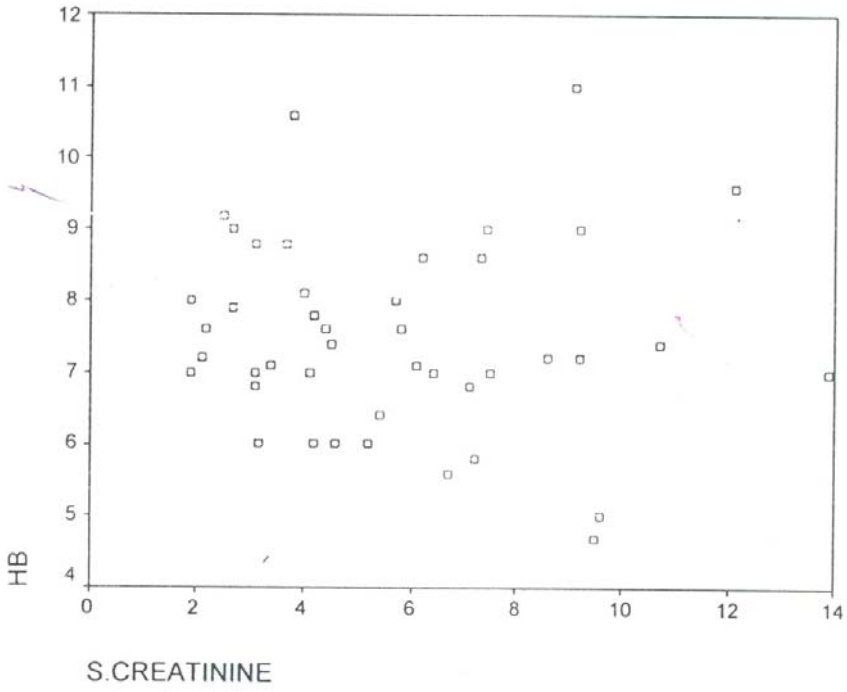


Hb values ranged from 4.7 to 10.6 g/dl with a mean value of 7.46 g/dl.



Serum creatinine:

Values ranged from 1.9 mg% to 13.9 mg% with a mean value of 5.6 mg%.



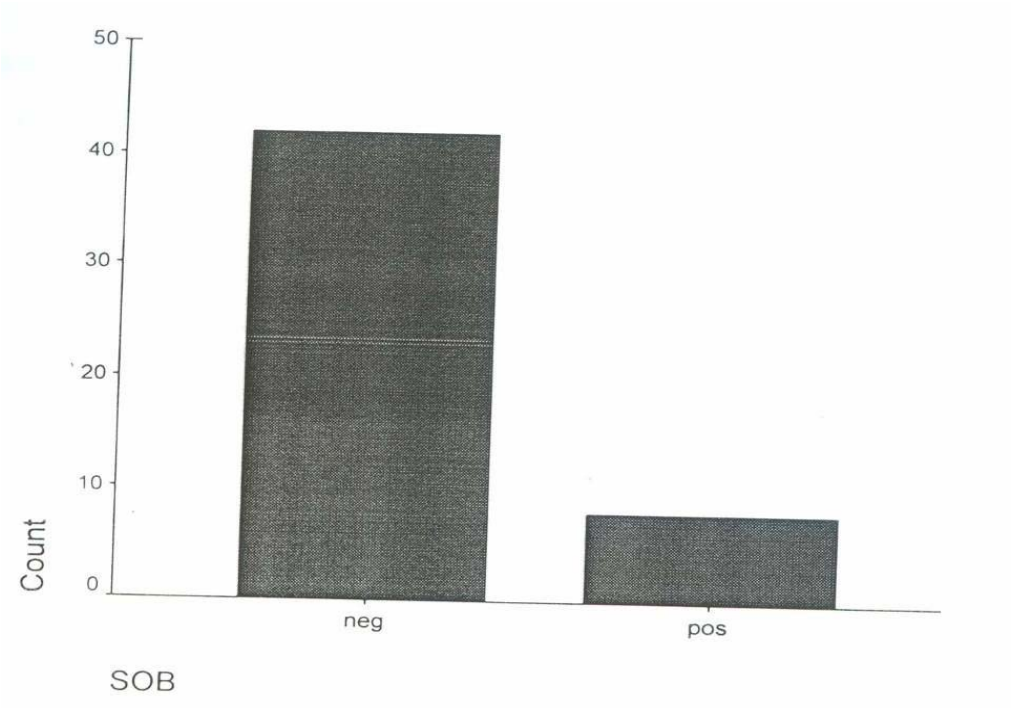
Serum Albumin:

Values ranged from 1.80 g/dl to 4.80 g/dl with a mean value of 3.6 g/dl.

Total protein:

Values ranged from 3.80 g/dl to 7.20 g/dl with a mean value of 6.2 g/dl.

Stool occult blood:



Serum cholesterol:

Values ranged from 110 mg% to 324 mg% with a mean value of 183 mg%.

Serum Alkaline phosphatase:

Values ranged from 81.4 IU to 743.0 IU with a mean value of 238 IU.

Serum Calcium:

Levels vary from 6.4 mg% to 12.0 mg% with a mean value of 9.1 mg%.

Serum Phosphorus:

Levels vary from 2.5 mg% to 15.1 mg% with a mean value of 5.2 mg%.

Serum Uric Acid:

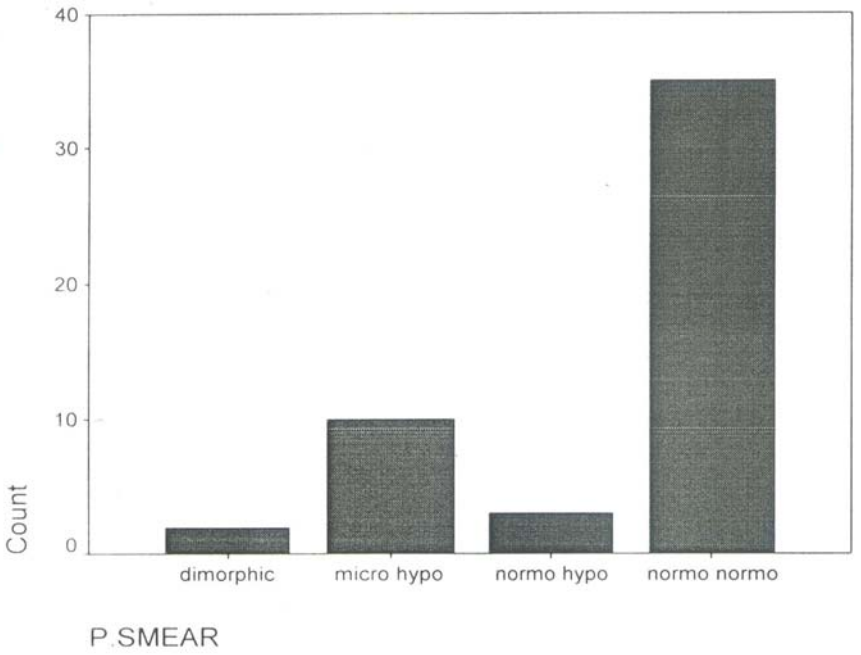
Levels vary from 3.0 mg% to 10.5 mg% with a mean value of 7.2 mg%.

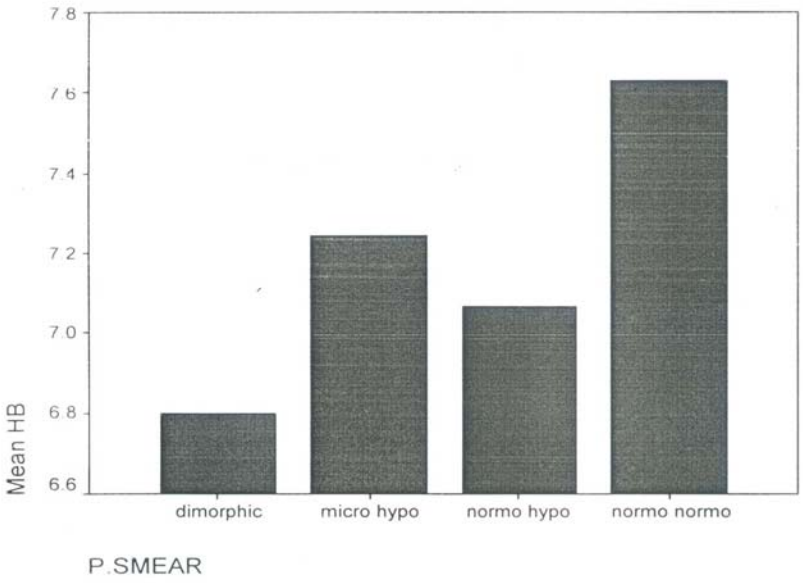
Serum Ferritin:

Levels vary from 130µg% to 1042 µg% with a mean value of 403.6 µg%.

Peripheral smear

Most frequent picture was normochronic normocytic. Also noted were dimorphic, normocytic hypochromic and microcytic anaemias.





PARTIAL CORRELATION COEFFICIENTS

Controlling for AGE

	HB	S.CREATININE
HB	**1.0000** **(0)**	**-.3115** **(38)**
S.CREATININE	**-.3115** **(38)**	**1.0000** **(0)**

P = .050

(Coefficient / (D.F.) / 2 tailed Significance)

PARTIAL CORRELATION COEFFICIENTS

Controlling for Hb

	S.CREATININE	S.PHOSPHORUS
S.CREATININE	**1.0000** **(0)**	**.4569** **(27)**
S.PHOSPHORUS	**.4569** **(27)**	**1.0000** **(0)**

P = .013

Controlling for HB

	S.CREATININE	S.FERRITIN
S.CREATININE	**1.0000 (0)**	**.9554 (2)**
S.FERRITIN	**.9554 (2)**	**1.0000 (0)**

P = .045

Controlling for Hb

	S.CREATININE	S.CHOLESTEROL
S.CREATININE	**1.0000 (0)**	**-.4563 (35)**
S.CHOLESTEROL	**-.4563 (35)**	**1.0000 (0)**

P = .005

DISCUSSION

In this study we have anaylsed 50 patients with chronic renal failure and having anaemia of whom 14 were females. Age of patients ranged from 15 to 77 years. Mean age of males was 47 years and that of females was 41 years. The mean hemoglobin level in males was 7.4 g% and that in females was 7.7 g%. None of them had prior treatment with erythropoietin for anaemia. All were excluded of having other serious systemic disorders. Few were on treatment with hemodialysis. All the patients were selected from Nephrology Department, Stanley Medical College and Hospital, Chennai-1.

Etiology for renal disease in our patients varied, most common being diabetic nephropathy which accounted from 28.6% cases. This is well in correlation with other world wide studies. Other important etiologies included chronic glomerulonephritis (22.2%), ADPKD (15.8%), Chronic tubulointerstitial disease (13.3%), IgA nephropathy (11%) and obstructive uropathy (6%). Hypertension, which is one of the commonest etiologies of CRF was not singly found as an etiological factor in our study, even though poorly controlled nypertension was present in a significant number of patients. This may be because only few of our patients underwent renal biopsy to have histological evidence for etiology. Also small sample size may be a factor for deviation from the general. In our study also ADPKD was the commonest etiological factor with monogenic inheritance.

Most of them in the study were having symptomatic moderate renal insufficiency. The commonest symptoms noted in our study were those due to mild anaemia, recurrent infections, loss of energy, decreased appetite, nocturia and early disturbance of nutritional status.

A significant inverse correlation was noted between serum creatinine and hemoglobin indicating that the severity of anaemia increases with renal failure. Other variables chosen for the study including stool occult blood (as marker for gastrointestinal blood loss), total protein, serum albumin, serum cholesterol (as indicators of nutritional status), Alkaline phosphatase, serum calcium or serum phosphorus and serum uric acid were not singly found to influence significantly this relation. Study population showed striking inter individual variability in progression to end stage renal disease irrespective of underlying etiology. Also it was noted that clinical symptom of uraemia were poorly correlating with elevated level of uraemic toxins.

One of the patients with a positive stool occult blood had third degree hemorrhoids for which local banding and hematinics were given improving her anaemia. Two thirds of those with stool occult blood positive had microcytic hypochromic anaemia. Since these patients have additional gastrointestinal blood loss and iron deficiency, correction of these with blood transfusion and iron supplementation will be the first treatment option when comparing the cost effectiveness of erythropoietin therapy. In our community since malnutrition is more prevalent, correction of anaemia with iron supplementation should be more effective than those proven western results.

Vast majority of the study population had normochromic normocytic blood picture in peripheral smear which is consistent with other well established studies. This proves that erythropoietin deficiency is the single most important causative factor of anaemia. The rest were having either microcytic hypochromic, dimorphic or normocytic hypochromic anaemia indicating associated blood loss, malnourishment or dialysis induced anaemia. Another significant observation was that the mean haemoglobin values in those with normochromic normocytic anaemia was significantly higher than that of those with other forms of anaemia indicating the presence of additional aetiologies like G.I. blood loss as indicated by positive stool occult blood, iron decifiency or malnutrition. Correction of these factors should improve the anaemia, and the symptoms and morbidity causes by it to a great extent. Erythropoetin therapy consists of twice weekly doses of 2000 IU for 6 to 8 weeks to achieve a target Hb level of at least 10 gm%. Thereafter, maintenance dose of 2000 IU is required once weekly. Each dose costs at least Rs.500/- and the therapy is to be continued life long. Concomitant parenteral iron therapy with once weekly elemental iron injections is mandatory. As most of the patients belong to low socio-economic strata and cannot afford life long erythopoetin therapy, correction of other causative factors would be a feasible approach in relieving their misery.

Significant inverse relation was found between serum cholesterol and serum creatinine levels indicating malnourishment in uremia. Relationship was also noted between serum creatinine and serum ferritin. This unexpected result can be attributed due to multiple blood transfusions received by those patients

with high ferritin. Serum creatinine and serum phosphorus levels also showed a direct relationship denoting the divalent ion metabolic abnormality of uraemia. Such a relationship was not met with S.Calcium and S.Creatinine, may be due to interference with frequent calcium and vitamin D supplementation.

Dialysis as a mode of treatment in renal disease improves the uremic milieu and is supposed to improve anemia also. But as dialysis can cause blood loss worsening anemia by:

1. Blood loss through tubings
2. Blood retention in the dialyser
3. Water treatment defects
4. Presence of chloramines in treated water
5. Multiple venepunctures
6. Temperature alterations leading to haemolysis

This may be the cause of anemia out of proportion to other uremic indicators in some of our patients who underwent dialysis. Additional factors causing anemia includes iron deficiency, blood loss from repeated lab tests, gastro intestinal bleeding usually from colitis, hyperparathyroidism, acute and chronic inflammatory conditions, Aluminum toxicity, folate deficiency, shortened red cell survival, hypothyroidism and rarely from underlying hemoglobinopathies.

Total protein, serum albumin and serum cholesterol are expected to be reduced in renal disease in proportion to reduction of haemoglobin. But such a relation was not met in this study. This may be accounted either by use of hemodialysis in some patients, multiple blood transfusions received by some of our patients or due to small study population.

Calcium and phosphorus are the major divalent ions involved in metabolic abnormalities of chronic renal diseases. High values of serum ferritin noted in some of our patients can be attributed to multiple blood transfusions received by them. The established inverse relation between serum uric acid and hemoglobin was not significantly proved, probably due to small sample size of the study. S.Sodium levels was not a chose variable among electrolyte profile since in chronic renal disease either sodium retention, wasting or maintenance of sodium balance can occur.

Since this study takes into consideration, only a small sample population, the results obtained from this study is to be confirmed by further larger studies.

CONCLUSIONS

This study indicates that:

1. Severity of anemia correlates well with the degree of renal disease.

2. Normochromic normocytic morphology anemia caused by erythropoietin deficiency is by far the commonest pattern.

3. Other morphologies in peripheral smear usually indicates presence of additional risk factors for anemia like blood loss, iron deficiency and malnutrition.

4. Presence of such risk factors is associated with significant reduction in mean haemoglobin values.

5. This suggests need for treatment of iron deficiency and correction of other anaemic risk factors in chronic renal disease.

6. Diabetic nephropathy is the commonest aetiology of chronic renal failure.

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PROFORMA

NAME AGE SEX IP/OP No.

ADDRESS OCCUPATION

PRESENTING COMPLAINTS

1.

2.

3.

H/O. PRESENTING COMPLAINTS

PAST HISTORY

GENERAL

H/O RENAL DISEASE

H/O TREATMENT TAKEN (including DIALAYSIS and TRANSFUSIONS)

HISTORY S/O ANAEMIA

PHYSICAL EXAMINATION

GENERAL EXAMINATION

Built and Norishment
Pallor
Skin
Nails
Oedema
Pulse rate
B P
J V P
Respiratory rate
Temperature
Eyes, Oral cavity
Asterixis

EXAMINATION OF

ABDOMEN

Skin changes
Palpable mass
Ascitis
Rectal examination
Renal bruit

CARDIOVASCULAR SYSTEM

Cardiomegaly
Added heart sounds
Arrhythmias
Basal crackles
Evidence of pericarditis
Vascular bruit

RESPIRATORY SYSTEM

Kussmaul's breathing
Additional sounds
Pleural effusion

CENTRAL NERVOUS SYSTEM

Evidence of uraemic encephalopathy
Evidence of peripheral neuropathy
Complication due to hypertension
Optic fundii

HAEMATOLOGICAL SYSTEM

Evidence of defective coagulation

WATER AND ELECTROLYTE IMBALANCE

Evidence of fluid overload

MUSCULOSKELETAL SYSTEM

Weakness
Bone pain
Bony deformities

PROVISIONAL DIAGNOSIS

INVESTIGATIONS

Hb		
WBC – TC	DC	ESR
PCV		
Platelet count		
Urinalysis		
Peripheral smear		
	S.Creatinine	
Blood urea		
S.electrolytes		
S.Uric acid		
Total protein	S.Albumin	ALP
S.Cholestrol		
TSH		
S.Fe	S.Ferritin	TIBC
ECG		

CXR

USG Abdomen

Echocardiography

Renal biopsy

Name	Age	Sex	Nature of renal disease	Hb	S.Creat	P.Smear	T.Protein

S.Albumin	S.Cholest	ALP	$S.Ca2^{+}$	S.Phos	S.Uric acid	S.Ferritin	TIBC	Stool Occ. Bld

MASTER CHART

S.No	Name	Age	Sex	Nature of Renal Disease	Hb	S.Creatinine	P.Smear	T.Protein	S.Albumin	S.Chol	ALP	S.Ca2+	S.P	S.Uric acid	S.Ferritin	TIBC	Stool Occult Blood
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1	Kantharubi	51	F	Sec FSGS	7	4.5	MH	4.4	2.2	120	142	10.6	2.5	3.5	162	444	-
2	Rajamuthu	40	M	ADPKD	6	12	NN	4.6	2.3	146	245	10.8	2.7	5.4	483	298	-
3	Varadhan	28	M	CGN	6.4	7.4	NH	3.9	1.8	162	290	11.9	3	6	444	267	-
4	Chelladurai	31	M	C/C TIN	8.4	4	NN	5.2	4.8	184	264	10.2	2.8	4.9	493	282	-
5	Gandhimathi	47	F	DM Nephr	4.7	2.6	MH	4	1.9	250	282	9.2	2.9	6.4	103	370	-
6	Udayakumar	15	M	IgA neph	7.5	3.2	NN	4.9	2.6	222	274	9	3.5	7.5	144	340	-
7	Valarmathi	46	F	DM Nephr	5	3.9	MH	5.6	2.2	242	294	7.2	6.4	7.8	178	475	+ve
8	Rose	28	F	CGN	8	5.6	NN	6	4	260	250	6.4	7	4.6	269	268	-
9	Premkumar	35	M	CGN	6.6	5.2	MH	6.2	4.1	142	264	6.9	7.2	6	163	369	+ve
10	Hemalatha	30	F	DM Nephr	8.6	7	NN	3.8	2.4	245	282	11.4	2.9	6.2	266	222	-
11	Rema	51	F	CGN	7.4	6.6	NN	6.1	4.5	124	164	6.6	8	6.5	335	229	-
12	Purushotham	69	M	Ischemic nephr	7	7	MH	5.9	4.2	178	224	6.3	7.1	4.8	132	562	+ve
13	Meena	55	F	ADPKD	6	2.9	MH	4.4	4	185	284	7.2	2.8	8.2	165	569	-
14	Neelakandan	72	M	DM Nephr	5.6	2.1	NN	3.8	2	270	296	7.8	6.9	4.9	289	442	-
15	Manikandan	67	M	Ischemic nephr	7.3	6.8	NN	4.2	2.6	194	264	6.8	6.6	5.2	360	360	-
16	Priya	28	F	C/C TIN	7	8.8	NN	4.8	2.8	225	268	7.9	3.3	7.2	335	383	-
17	Mallika	54	F	DM Nephr	6	9.5	NH	4.1	2.6	292	184	6.5	7.9	4.2	169	320	-
18	Suresh	65	M	Ischemic nephr	7.6	8.9	NN	5.5	2	184	289	7.8	3	4.3	285	351	-
19	Mohanbabu	52	M	DM Nephr	7	11	NN	5.4	2.3	324	273	6.7	10	6.8	265	380	-
20	Sarammal	55	F	CGN	7.3	12.3	NN	6.2	3.2	260	242	7.5	8.2	6.9	278	302	-
21	Mumtaz	22	F	CGN	7.6	12.6	NN	6.4	3.2	198	216	7.9	6.8	6.2	468	325	-
22	Sasikumar	25	M	IgA neph	7.8	1.9	MH	6.3	3.5	150	172	7.4	6.5	6.9	130	460	+ve
23	Parimala	55	F	DM Nephr	6	10.3	NH	4	2.2	294	238	8	5.6	7.2	256	309	-
24	Ramu	26	M	C/C TIN	8	4.2	DA	7.2	3.6	205	222	8.5	5.9	8.8	222	340	-
25	Narendran	65	M	DM Nephr	7	5.3	NN	6.9	2.9	264	194	8.2	5.75	8.6	502	365	-
26	Mustaqkhan	56	M	ADPKD	7.3	5.9	NN	7.2	4.2	192	205	6.5	5.28	9	562	348	-ve
27	Moorthy	55	M	ADPKD	7.1	3.3	NN	6.6	3.8	180	164	7.3	6.6	9.5	493	369	-
28	Habela	34	F	CGN	6	6.6	DA	4.5	3	165	256	7.2	7.4	10.5	160	382	-
29	Venkateshwaran	60	M	DM Nephr	6.8	5.8	MH	7	3.2	295	284	11.8	5.1	8	122	396	+ve

S.No	Name	Age	Sex	Nature of Renal Disease	Hb	S.Creatinine	P.Smear	T.Protein	S.Albumin	S.Chol	ALP	S.Ca2+	S.P	S.Uric acid	S.Ferritin	TIBC	Stool Occult Blood
30	Ravi	60	M	SOLITARY KIDNEY	7.9	4	NN	6.8	3.6	160	564	12	3.2	9.4	602	335	-
31	Govindaraj	60	M	OBSTRUCTIVE UROPATHY	5.2	6.2	NN	4.6	2	149	256	8.6	7	7	545	336	-
32	Ghouse basha	48	M	CGN	6.8	7.7	NH	4.4	2.2	220	324	9.2	2.9	7	402	295	+ve
33	Pushpa	56	F	CGN	6.2	6.9	NN	4.8	2.1	240	131	6.8	15.1	6.9	666	278	-
34	Ajmilkhan	19	M	ADPKD	6.6	7.3	NN	5.2	3.9	146	260	9.9	5.1	7.2	646	303	-
35	Palanivel	35	M	C/C TIN	8.8	2.6	NN	5.5	3.6	172	420	9.4	5.2	7.8	660	256	-
36	Vijayan	20	M	DM Nephr	6.5	10.2	MN	6	2.5	149	444	9.6	4.9	7.1	133	483	-
37	Muthusamy	45	M	IgA neph	9.4	2.2	NN	4.9	2.9	182	424	11.2	4.2	6.2	180	373	-
38	Ramasamy	59	M	DM Nephr	6.8	6.8	NH	5.2	3	165	165	7.6	7.9	3.5	393	325	-
39	Raja	56	M	ADPKD	8.9	4.3	NN	2.5	1.8	122	90	8	6.5	3.7	405	330	-
40	Ramu	48	M	ADPKD	6.2	2.9	NN	5.3	2.2	190	94	8.2	7.8	4	385	362	-
41	Ramadoss	77	M	OBSTRUCTIVE UROPATHY	7	5.6	NH	3.3	1.9	162	89	6.8	7.8	4.9	162	313	-
42	Habela	18	F	C/C TIN	8	2.8	MH	4.5	2.2	140	154	9	7.9	6.8	102	466	-
43	Alagappan	42	M	DM Nephr	6.5	7.2	DA	6.5	3.5	220	168	8.9	5.5	6.6	122	330	-
44	Chinnasamy	49	M	CGN	7	8.5	DA	7.2	4	185	222	7.2	5.8	7.4	106	304	-
45	Govindaraj	16	M	IgA neph	6.9	9.2	NN	7	3.7	126	320	7.8	6.2	7.8	483	363	-
46	Kuppusamy	50	M	DM Nephr	6	4	DA	4.4	2.9	225	149	6.4	6.9	8.2	128	498	-
47	Ezhumalai	40	M	C/C TIN	10	4.2	NN	4.5	2.2	124	278	9.6	5.5	6.9	496	420	-
48	Punniyakotti	50	M	DM Nephr	5.4	6	NH	6.2	3.2	165	562	11.2	5.2	7.1	138	390	-
49	Palani	34	M	CGN	7	2.9	MH	7	3.6	184	440	10.2	5	7.6	166	660	-
50	Raja	48	M	ADPKD	4.8	11	MH	7.1	3.8	192	429	11	3	7.2	182	487	-

NN - **Normocytic Normochromic**
NH - **Normocytic Hypochromic**
MH - **Microcytic Hypochromic**
S. Ca2 - **Serum Calcium**
ALP - **Alkaline Phosphatase**
SP - **Serum Phosphorus**
TIBC - **Total Iron Binding Capacity**
CGN - **Chronic Glomerulonephritis**
C/C TIN - **C/C Tubulointerstitial disease**
ADPKD - **Adult Polycystic Kidney Disease**