Intravenous Levocarnitine Reduces Erythropoiesis-Stimulating Agent Requirements and Improves Anaemia Indices in Maintenance Haemodialysis Patients: A Prospective Cohort Study.

Shazia Abbas[1], Mateen Akram[2], Sibgha Ahmed[3], Sameer Sattar[4], Palwisha Ameen[5*], Muhammad Usman Masood Butt[6].

ABSTRACT:

Objective: To determine whether adding levocarnitine to individuals on maintenance haemodialysis lowers the need for Erythropoiesis-stimulating agents (ESAs) while preserving hematologic control.

Methodology: This prospective observational cohort study was conducted at the Department of Nephrology, Shaikh Zayed Hospital, Lahore, from July to December 2025. Adults on thrice-weekly hemodialysis were enrolled into an exposed cohort receiving levocarnitine 1,000 mg intravenously after dialysis three times weekly and an unexposed cohort receiving no levocarnitine. Both groups received recombinant human erythropoietin according to a standardized titration protocol. Haemoglobin (Hb), hematocrit (Hct), weekly ESA dose, and erythropoietin responsiveness index (ERI = weekly ESA dose ÷ [dry weight × average Hb]) were recorded monthly for six months.

Results: Ninety-four patients were included (47 each cohort). Baseline characteristics were generally comparable, although controls were older, heavier, and had slightly higher baseline Hct. No clear advantage was seen at Month 1. From Month 2 onward, levocarnitine was associated with higher Hb and Hct and lower ESA dose. By Month 6, Hb was 12.00 vs 9.77 g/dL, Hct 36.19% vs 29.29%, weekly ESA dose 7,715 vs 11,094 units, and ERI 10.07 vs 17.36 (all $p<0.0001$).

Conclusion: Adjunctive levocarnitine improved erythropoiesis efficiency and reduced ESA requirements over six months.

Keywords: anaemia; erythropoiesis-stimulating agents; erythropoietin responsiveness index; haemodialysis; levocarnitine.

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Introduction:

Anaemia is a pervasive and clinically consequential complication of chronic kidney disease (CKD), particularly among patients on maintenance haemodialysis (HD).[1] Contemporary CKD guidance emphasizes correction of reversible contributors to anaemia, including iron deficiency, inflammation, nutritional deficits, hyperparathyroidism, and medication-related factors, before escalation of erythropoiesis-stimulating agent (ESA) therapy.[2] Current CKD frameworks also stress individualized treatment strategies to balance haemoglobin targets against cardiovascular and thromboembolic risks.[3] In the setting of a growing dialysis population with substantial symptom burden and impaired quality of life, strategies that safely reduce ESA exposure while preserving haematologic control are increasingly important.[4]

ESA hypo-responsiveness remains a common and prognostically adverse problem in HD.[5] It is multifactorial, frequently influenced by iron status, inflammation, dialysis adequacy, nutritional status, and mineral-bone disease. [6] Escalating ESA doses to overcome resistance has been associated with adverse cardiovascular outcomes, reinforcing the importance of interventions that improve erythropoietic efficiency rather than merely increasing drug exposure. [7] Levocarnitine (L-carnitine), a dialyzable quaternary amine involved in mitochondrial fatty acid transport, is often depleted in long-term HD, and carnitine deficiency has been linked to erythropoietin-resistant anaemia, impaired erythrocyte deformability, oxidative stress, and reduced cellular energy metabolism.[8] Few randomized and observational studies have reported variable improvements in haemoglobin levels and reductions in ESA requirements with levocarnitine supplementation, although heterogeneity in study design, dosing strategies, and patient selection has limited definitive conclusions.[8] In Pakistan, the burden of CKD and end-stage renal disease is increasing within a resource-constrained healthcare environment where ESA therapy represents a substantial recurring cost to hospitals and families.[7] Despite this, there is a paucity of prospective local data evaluating dose-sparing strategies for anaemia management in maintenance HD.[7] Cost containment without compromising haematologic outcomes is a pressing clinical and policy priority.[7]

1. Trainee, Department of Nephrology, Shaikh Zayed Hospital, Lahore, Pakistan.
2. Associate professor, Department of Nephrology, Shaikh Zayed Hospital, Lahore, Pakistan.
3. Trainee Registrar, Department of Nephrology, Shaikh Zayed Hospital, Lahore, Pakistan.
4. Trainee Registrar, Department of Nephrology, Shaikh Zayed Hospital, Lahore, Pakistan.
5. Post graduate resident, Department of Nephrology, Shaikh Zayed Hospital, Lahore, Pakistan.
6. Department of Nephrology, Shaikh Zayed Hospital, Lahore, Pakistan.

**=corresponding author :*
Email: palwashaa232@gmail.com

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The novelty of the study is that this is one of the few prospective cohort studies from Pakistan evaluating intravenous levocarnitine specifically as a dose-sparing adjunct in maintenance haemodialysis. Second, the study applies a standardized ESA titration algorithm across both cohorts, allowing meaningful assessment of true responsiveness rather than uncontrolled prescribing variability. Third, erythropoietin responsiveness index (ERI) was calculated serially and analysed longitudinally over six months, enabling time-dependent evaluation of erythropoiesis efficiency. Fourth, the study examines sustained divergence in ESA requirements using repeated-measures modelling, rather than relying on single end-point comparisons. Finally, the work contextualizes clinical outcomes within a resource-limited dialysis system, highlighting potential economic implications alongside haematologic efficacy. Collectively, these features address important methodological and contextual gaps in the existing literature. Therefore, this study aimed to evaluate whether adjunctive intravenous levocarnitine reduces erythropoiesis-stimulating agent (ESA) requirements and improves anaemia indices in patients on maintenance haemodialysis over six months.

Methodology:

This prospective observational cohort study was conducted in the Department of Nephrology, Shaikh Zayed Hospital, Lahore, over six months. The sample size was calculated using the WHO sample size calculator for comparison of two independent means. Based on the expected difference in weekly ESA dose from previously published data, with a two-sided 5% level of significance, 80% power, and 1:1 allocation, the required sample size was 47 participants in each group. Therefore, a total of 94 patients were included in the study.[9]

Inclusion criteria comprised of adults 18–80 years receiving thrice-weekly maintenance hemodialysis for ≥3 months, clinically stable for ≥4 weeks with no change in dialysis prescription beyond routine adjustments, on anemia management with ESAs (stable ESA dose ≥4 weeks or documented ERI from the preceding month), screening hemoglobin within the program's target range (≈8.0–11.5 g/dL), iron replete or corrected per local criteria, and adequate dialysis (e.g., spKt/V ≥1.2). Ability to provide informed consent and to complete six months of monthly follow-up was required.

Key exclusions included active intercurrent illness, infection, or marked inflammation; recent (≤3 months) transfusion, major surgery, or overt bleeding; uncorrected iron, folate, or vitamin B12 deficiency; hematologic disorders (e.g., haemoglobinopathies), bone-marrow failure, or active malignancy on cytotoxic/marrow-suppressive therapy; uncontrolled secondary hyperparathyroidism requiring urgent intervention; severe hepatic dysfunction, decompensated heart failure, uncontrolled hypertension, or clinically significant arrhythmia; pregnancy or lactation; hypersensitivity to levocarnitine or therapeutic carnitine use within 3 months; planned transplant, change of dialysis modality, relocation, or concurrent interventional study; contraindications to ESA therapy under local policy; and any condition likely to compromise protocol adherence, safety monitoring, or outcome validity.

Consecutive adults (18–80 years) on maintenance hemodialysis for ≥3 months with renal anemia were enrolled after written informed consent. Patients were classified into an "exposed" cohort (treated with levocarnitine 1,000 mg intravenously post-dialysis, three times weekly, as per treating physician's decision) and an "unexposed" cohort (no levocarnitine). Baseline demographics, comorbidities, dialysis details, dry weight, hemoglobin (Hb), and hematocrit (Hct) were recorded, and participants were followed monthly for six months to capture Hb, Hct, erythropoiesis-stimulating agent (ESA) dose, adverse events, and the erythropoietin responsiveness index (ERI), defined as monthly ESA dose (Units) divided by [dry weight (kg) × average Hb (g/dL)].

Patients allocated to the exposed group received levocarnitine 1,000 mg intravenously three times weekly immediately after dialysis, while both groups received recombinant human erythropoietin (rHuEPO) according to a standardized algorithm guided by hemoglobin/hematocrit and the erythropoietin responsiveness index (ERI). Initial ESA dosing followed prespecified ranges (higher doses for Hb <10 g/dL/Hct <30%, tapering for maintenance at Hb 11–12 g/dL or Hct 33–36%), with titration rules to reduce ESA by 25% if Hb rose >1 g/dL within two months, maintain dosing when Hb remained 10–12 g/dL, and increase by 25% if Hb persisted <10 g/dL or Hct <30% after two months. The primary endpoint was ESA requirement and ERI. A structured proforma captured monthly (months 1–6) Hb, Hct, ESA dose, and ERI, alongside adverse events and dialysis -related details as per the form.

Ethical Approval:

Ethical approval for this study was granted by the Technical & Ethical Review Committee (TERC), Institutional Review & Research Advisory Board (IRRAB), Shaikh Zayed Medical Complex, Lahore (TERC ID: TERC/SC/INT/2025/455; approval date 14-07-2025).

Statistical Analysis:

Data were analysed using SPSS version 27.0. Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequency and percentage. Independent-samples t-test was used to compare baseline continuous variables between the Levocarnitine (LVC) and Control (CTL) groups. These variables included age, height, weight, body mass index, Haemoglobin, and haematocrit. This test was applied to determine whether the two groups were comparable at baseline. Chi-square test was used to compare categorical variables such as hypertension and diabetes mellitus between the two groups. Fisher's exact test was applied when the expected cell count was small. These tests were used to assess whether the distribution of comorbidities was similar in both groups. For month-wise comparisons of Haemoglobin, haematocrit, ESA dose, and erythropoietin resistance index (ERI), independent-samples t-test was used at each time point. This test was applied to compare the LVC and CTL groups separately at each month. To check the difference between the Levocarnitine (LVC) and Control (CTL) groups, Two-Way Repeated Measures ANOVA was performed. Mauchly's test of sphericity was used to assess the sphericity assumption for the within-subject factor (time). As the assumption of sphericity was violated, the Greenhouse-Geisser correction was applied for interpretation of the repeated-measures results. A p-value of less than 0.05 was considered statistically significant.

Results:

Demographic characteristics of both groups are shown in table 1. The independent-samples t-test was applied to compare baseline continuous variables between the Levocarnitine and Control groups. The control group was significantly older and had higher body weight than the levocarnitine group. Baseline hematocrit was also significantly higher in the control group. However, height, BMI,

and baseline Hemoglobin were not significantly different between the two groups.

Table No 1. Baseline characteristics of the study groups.

Variable	Levocarnitine (n=47)	Control (n=47)	p-value
Age (years)	50.45 ± 8.36	56.17 ± 9.64	0.0028*
Height (cm)	162.53 ± 7.72	161.87 ± 7.92	0.6836
Weight (kg)	62.74 ± 7.90	66.12 ± 7.17	0.0324*
BMI (kg/m²)	23.92 ± 3.81	25.39 ± 3.60	0.0580*
Baseline Hb (g/dL)	8.79 ± 0.31	8.87 ± 0.32	0.1849
Baseline Hct (%)	26.01 ± 1.45	26.74 ± 1.51	0.0191*

Data are presented as mean ± SD. p-values were calculated using the independent-samples t-test; Welch's t-test was applied when the assumption of equal variances was violated. P < 0.05 was considered statistically significant. * Indicates statistically significant difference between groups.

The comparison of categorical baseline variables between the two groups is shown in table2. Chi-square test or Fisher's exact test was used to assess whether the distribution of comorbidities differed between the Levocarnitine and Control groups. Overall, hypertension and diabetes mellitus were not significantly different between groups. In sex-stratified analysis, hypertension remained comparable in both males and females. Diabetes mellitus was significantly more frequent among females in the levocarnitine group, while no significant difference was found among males.

Table No 2. Comorbidities overall and by sex.

Variable	Control	Levocarnitine	p-value
Overall hypertension	39/47 (83.0%)	34/47 (72.3%)	0.3221
Overall diabetes mellitus	19/47 (40.4%)	25/47 (53.2%)	0.3014
Hypertension (Females)	16/22 (72.7%)	12/18 (66.7%)	0.7385
Hypertension (Males)	23/25 (92.0%)	22/29 (75.9%)	0.1531
Diabetes mellitus (Females)	8/22 (36.4%)	13/18 (72.2%)	0.0309*
Diabetes mellitus (Males)	11/25 (44.0%)	12/29 (41.4%)	1.0000

Data are presented as n (%). P-values were calculated using Pearson's chi-square test; Fisher's exact test was applied when any expected cell count was less than 5. P < 0.05 was considered statistically significant. * Indicates statistically significant difference between groups.

Table 3 shows the month-wise comparison of Hb, Hct, ESA dose, and ERI between the two groups. Independent-samples t-test was used at each time point to compare the Levocarnitine and Control groups separately for each outcome. At Month 1, Hemoglobin was slightly higher in the control group, while hematocrit and ESA dose were not significantly different. ERI was significantly higher in the levocarnitine group at Month 1. From Month 2 onward, Hemoglobin and hematocrit became significantly higher in the levocarnitine group. From Month 3 onward, ESA dose and ERI became significantly lower in the levocarnitine group. By Month 6, all outcomes showed significant improvement in favor of the levocarnitine group.

Table No. 3: Monthly outcomes in both groups.

Outcome / Time	Levocarnitine (Mean ± SD)	Control (Mean ± SD)	p-value
Hb (g/dL)			
Month 1	8.78 ± 0.27	8.90 ± 0.30	0.0403
Month 2	9.44 ± 0.25	9.05 ± 0.27	<0.0001*
Month 3	10.02 ± 0.29	9.23 ± 0.30	<0.0001*
Month 4	10.75 ± 0.32	9.42 ± 0.29	<0.0001*
Month 5	11.36 ± 0.30	9.58 ± 0.33	<0.0001*
Month 6	12.00 ± 0.38	9.77 ± 0.33	<0.0001*
Hct (%)			
Month 1	26.14 ± 1.24	26.66 ± 1.42	0.0611
Month 2	28.41 ± 1.40	27.29 ± 1.32	0.0001*
Month 3	30.06 ± 1.32	27.93 ± 1.40	<0.0001*
Month 4	32.24 ± 1.26	28.57 ± 1.43	<0.0001*
Month 5	34.14 ± 1.39	28.92 ± 1.49	<0.0001*
Month 6	36.19 ± 1.23	29.29 ± 1.32	<0.0001*
ESA dose (units/week)			
Month 1	12174.47 ± 1170.42	11968.09 ± 1297.88	0.4203
Month 2	11287.23 ± 1171.00	11804.26 ± 1349.51	0.0503
Month 3	10410.64 ± 1079.40	11621.28 ± 1338.87	<0.0001*
Month 4	9445.74 ± 980.29	11468.09 ± 1366.34	<0.0001*
Month 5	8659.57 ± 1006.70	11244.68 ± 1463.85	<0.0001*
Month 6	7714.89 ± 1053.66	11093.62 ± 1366.11	<0.0001*
ERI			
Month 1	22.46 ± 3.98	20.57 ± 2.78	0.0091*
Month 2	19.34 ± 3.53	19.92 ± 2.69	0.3720
Month 3	16.82 ± 3.08	19.27 ± 2.73	<0.0001*
Month 4	14.25 ± 2.65	18.63 ± 2.70	<0.0001*
Month 5	12.35 ± 2.33	17.93 ± 2.63	<0.0001*
Month 6	10.07 ± 2.00	17.36 ± 2.46	<0.0001*

*Data are presented as mean ± SD. P-values at each monthly time point were calculated using the independent-samples t-test; Welch's t-test was applied when the assumption of equal variances was violated. Hb = haemoglobin; Hct = haematocrit; ESA = erythropoiesis-stimulating agent; ERI = erythropoietin responsiveness index. P < 0.05 was considered statistically significant. * Indicates statistically significant difference between groups.*

Two-Way Repeated Measures ANOVA showed significant effects of time, group, and time × group interaction for all longitudinal outcomes (Table 4). For haemoglobin, there were significant effects of time ($F(1.08, 99.64) = 2121.36$, $p < 0.001$), group ($F(1, 92) = 379.04$, $p < 0.001$), and time × group interaction ($F(1.08, 99.64) = 701.45$, $p < 0.001$). For haematocrit, significant effects were also observed for time ($F(1.86, 171.25) = 464.16$, $p < 0.001$), group ($F(1, 92) = 251.42$, $p < 0.001$), and time × group interaction ($F(1.86, 171.25) = 154.77$, $p < 0.001$). Similarly, weekly ESA dose showed significant effects of time ($F(1.18, 108.90) = 874.06$, $p < 0.001$), group ($F(1, 92) = 41.42$, $p < 0.001$), and time × group interaction ($F(1.18, 108.90) = 390.25$, $p < 0.001$). ERI also showed significant effects of time ($F(1.13, 103.93) = 1024.22$, $p < 0.001$), group ($F(1, 92) = 29.71$, $p < 0.001$), and time × group interaction ($F(1.13, 103.93) = 348.35$, $p < 0.001$).

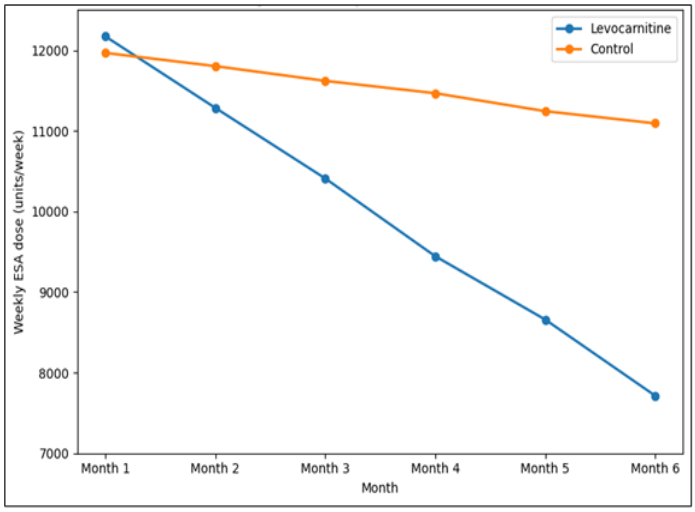
Table No 4: Two-way repeated-measures ANOVA.

Outcome	Effect	F (df1, df2)	p-value	Partial η^2
Haemoglobin	Time	F (1.08, 99.64) = 2121.36	<0.001*	0.958
	Group	F (1, 92) = 379.04	<0.001*	0.805
	Time × Group	F (1.08, 99.64) = 701.45	<0.001*	0.884
Haematocrit	Time	F (1.86, 171.25) = 464.16	<0.001*	0.835
	Group	F (1, 92) = 251.42	<0.001*	0.732
	Time × Group	F (1.86, 171.25) = 154.77	<0.001*	0.627
Weekly ESA dose	Time	F (1.18, 108.90) = 874.06	<0.001*	0.905
	Group	F (1, 92) = 41.42	<0.001*	0.310
	Time × Group	F (1.18, 108.90) = 390.25	<0.001*	0.809
ERI	Time	F (1.13, 103.93) = 1024.22	<0.001*	0.918
	Group	F (1, 92) = 29.71	<0.001*	0.244
	Time × Group	F (1.13, 103.93) = 348.35	<0.001*	0.791

*Results are presented as F-statistic, p-value, and partial η^2 from Two-Way Repeated Measures ANOVA. Mauchly's test of sphericity showed violation of the sphericity assumption for all longitudinal outcomes; therefore, Greenhouse-Geisser corrected results were used for the within-subject effect of time and the time × group interaction. P < 0.05 was considered statistically significant. * indicates statistically significant effect.*

Figure 1 shows the trend in weekly ESA dose from Month 1 to Month 6 in both groups. In the levocarnitine group, the ESA dose decreased steadily over time. In the control group, the ESA dose showed only a slight reduction. The gap between the two groups became wider with each month. By Month 6, the levocarnitine group required a much lower ESA dose than the control group. This pattern supports the finding that levocarnitine reduced ESA requirement over time.

Figure No 1: Weekly ESA dose over time in the Levocarnitine and Control groups. Values represent mean weekly ESA dose (units/week) from Month 1 to Month 6.



Discussion:

Current study demonstrates that adjunctive levocarnitine in maintenance haemodialysis is associated with progressively higher haemoglobin and haematocrit alongside lower weekly ESA dose and improved erythropoietin responsiveness (ERI), with separation emerging by Month 2 and consolidating through Month 6.[6] The pattern suggests a clinically meaningful dose-sparing effect without loss of anaemia control, aligning with biologic plausibility in carnitine-depleted dialysis patients and with contemporary evidence that prioritizes improving erythropoiesis efficiency over escalating ESA exposure.[8,10]

The present findings are concordant with recent syntheses indicating that carnitine repletion can enhance erythrocyte energy handling and membrane stability, reduce oxidative stress, and thereby augment marrow sensitivity to ESA.[8] Consistent between-group advantages from Month 3 onward mirror signals from contemporary clinical and observational literature in HD showing that ESA hyporesponsiveness is clinically relevant and that improved responsiveness may translate into better outcomes, although prior results have varied with dose, route, and baseline deficiency.[11,12] In a recent meta-analysis that focused on haemodialysis populations, carnitine supplementation was linked to reduced ESA requirements and improved ERI, even where haemoglobin gains were modest.[6] Evidence examining oxidative stress, inflammation, and nutritional status in HD also supports the concept that erythropoietic responsiveness is biologically modifiable rather than fixed.[13,14] Observational data from dialysis cohorts further show that ERI is influenced by iron handling, inflammation, mineral metabolism, and nutritional status, which is consistent with the time-dependent improvement observed here.[4,5,15] Moreover, updated overviews in CKD support a role for targeted rather than universal adjunctive strategies in patients with ESA hypo-responsiveness which is consistent with the pragmatic add-on use evaluated in this cohort.[1,10]

Not all literature agrees on the magnitude or certainty of effect.[8] Some studies and reviews reported heterogeneity related to formulation, dose, dialysis clearance, duration of therapy, adherence, and patient selection.[6,8] Differences in ESA protocols, iron stewardship, inflammatory burden, and

body composition may also confound between-study comparisons.[14,16,17] Nonetheless, when dosing is adequate and treatment is continued for several weeks, the balance of recent evidence supports a dose-sparing potential for levocarnitine and related adjunctive approaches, particularly beyond 8-12 weeks of therapy, matching the delayed yet sustained divergence observed across Months 3-6.[6,18]

Several design features strengthen interpretability, including prospective ascertainment, consistent dialysis schedules, standardized ESA titration rules, and monthly capture of Hb, Hct, and ESA permitting ERI estimation.[10] Still, important limitations apply. This was a single-centre, non-randomized cohort with modest sample size and six-month follow-up; causal inference is therefore limited, and residual confounding cannot be excluded.[10,11] Baseline imbalances, including older age, greater weight, and slightly higher baseline haematocrit in controls, as well as higher diabetes prevalence among females in the levocarnitine arm, may have influenced estimates despite stable early outcomes and the later direction of effect.[16,17] Unmeasured covariates, including inflammatory activity, parathyroid control, oxidative stress, micronutrient status, and detailed iron kinetics, could also have contributed to ESA dynamics.[14] Free carnitine and acylcarnitine levels were not measured, precluding phenotype-guided analysis.[8] Safety endpoints beyond routine adverse-event capture and patient-reported outcomes were not systematically assessed, and no formal cost-effectiveness modelling was undertaken.[10]

Conclusion:

Adjunctive levocarnitine improved erythropoiesis efficiency and reduced ESA requirements over six months.

Conflict of Interest: None
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Data Sharing Statement: Data shall be provided by the corresponding author upon reasonable request.

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Authors' Contribution	
Shazia Abbas	Conception of study, study design, data acquisition & analysis, manuscript drafting
Mateen Akram	Supervision of study, study design, interpretation of data, critical review
Sibgha Ahmed	Data collection, interpretation of data, manuscript drafting
Sameer Sattar	Data collection, data acquisition support, manuscript drafting
Palwisha Ameen	Data collection, critical review, manuscript drafting
Muhammad Usman	Data collection, critical review, manuscript drafting
All authors approved the final version to be published and agreed to be accountable for all aspects of the work, ensuring that any questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.	