cological classes. It also suggests avenues that should not be overlooked when investigating new drugs or improving older medications. The results demonstrate that many relatively insoluble drugs may be readily formulated in soft elastic capsules and have faster dissolution rates than tablets in that solutions or suspensions of a drug can be readily encapsulated. Furthermore, surfactants or other compounds may be encapsulated along with the drug so as to enhance its solubility and potential absorption rate. Soft elastic capsules are recommended in the formulations of low-dose medication, of relatively insoluble drugs, and of drugs where early high-blood level of the drug is indicated.

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# *DRUG STANDARDS*

# Chemical Standardization and Quality Assurance of Whole Crude Coal Tar USP Utilizing GLC Procedures


**M. GRUBER, R. KLEIN, and M. FOXX**



**Abstract** □ A procedure has been developed which utilizes gas-liquid chromatographic (GLC) analysis for the chemical standardization of medicinal crude coal tar USP. A similar method is recommended for the determination of coal tar fractions in Liquor Carbonis Detergens (LCD) (coal tar solution USP). Data confirming that LCD and similar "extracts," "fractionates," and "synthetics" cannot be considered as generic, pharmaceutical, or medicinal equivalents of a properly standardized whole crude coal tar are presented.



**Keyphrases** □ Crude coal tar—analysis □ Coal tar solution—analysis □ Ethanol content, coal tar solution—determination □ GLC—analysis.


Dioscorides, a Greek physician, described nearly 2000 years ago the merits of asphaltic tar in the "Materia Medica" as a treatment for cutaneous disorders (1). The advantages of the empirical use of "tars" were subsequently emphasized by numerous investigators including Brocq (2), White (3), and Goeckerman (4, 5).

In modern times, this medication is widely prescribed for various skin diseases, such as psoriasis and eczema, which are frequently severe and occasionally disabling. In addition, this modality is routinely prescribed for seborrheic dermatitis, occupational and contact dermatitis, dermatophytosis, varicose eczema, chronic and exudative and lichenoid dermatitis, pruritis ani, and various other chronic skin disorders.

Although therapeutic response is often dramatic, the known variability of coal tar composition and consequent inconsistency of clinical results has made this medication the subject of complaint and controversy among dermatologists.

This ancient but fundamental topical drug is virtually devoid of any guardian standards of chemical composition. Consequently, almost any coal tar, regardless of its composition, may satisfy the requirements of current official compendia for crude coal tar. Practically no controls have been established to assure uniformity, potency, safety, and efficacy. It is, therefore, quite evident that the scientific development of far more definitive drug reference standards and methods of analysis for this valuable, but variable, therapeutic agent is mandatory. No proficient effort has been initiated to create an effective method to control the physical and

chemical properties of this medicinal substance with the exception of an exploratory investigation by de Martin and Cyr in 1953 (6).

## GENERAL CHARACTERISTICS

Crude coal tar is an extremely complex by-product of the destructive distillation of coal. There are uncontrolled qualitative and quantitative chemical and pharmacological differences, dependent upon the source of raw material, method, and temperature of distillation, shape and size of retorts, and other factors (7). Accordingly, since the medicinal qualities of this material are dependent upon the aggregate effect of its hundreds of discrete components, many of which have never been identified, considerable variations in clinical results are apparently unavoidable. A lack of uniformity and the variations in therapeutic effect of different coal tars have caused concern (8).

All attempts to retain the therapeutic effects, while simultaneously removing the objectionable black color, odor, and staining properties of coal tar, have been futile, although it has been "fractionated," "separated," "extracted," "filtered" and "synthesized" to improve its esthetic appearance. The relatively clear substances which have emerged possess one common deficiency, namely a considerable reduction of pharmacological activity caused by the removal of the "objectionable" tar fractions including pitch, carbon, and asphaltic compounds (9).

Even its mode of action has not been satisfactorily defined, having been variously described as "reducing," "photosensitizing," "irritant," "antiseptic," "antipruritic," "keratoplastic," "antiacanthotic," "vasoconstrictive," "antiparasitic," "antifungal," and "antibacterial."

Coal tar is described in the USP XVII as a "nearly black, viscous liquid, heavier than water, having a characteristic, naphthalene-like odor and a sharp, burning taste" (10). These vague descriptions have only compounded the physician's problem of attempting to obtain consistent and uniform clinical results.

The monograph on LCD (coal tar solution USP) is equally obscure (11). The only quantitative specification is for alcohol concentration. This permits enormous variation in the tar-extract content and the incorporation of such dissimilar constituents as to make this qualification virtually meaningless.

For the past 15 years, the authors' control laboratory has employed, with some success, the methods introduced by de Martin and Cyr (6). These techniques considerably improved quality and uniformity, but were inadequate for assuring a specific, chemically standardized, medicinal "whole" coal tar. During the past 2 years, the authors' have utilized GLC to achieve this goal.[1]

Other attempts have been made to standardize the therapeutic response which physicians could reasonably anticipate from tar by comparing relative bioassays or measurements of the photodynamic action of tar on normal guinea pig skin (12). Photobiological activity as the quality control determinant of tar, manifested by sensitization effects on human, rabbit, guinea pig, or other mammalian skin, is deceiving since this attribute of coal tar is related primarily to its anthracene–acridine content (9). The fluorescence under longwave UV light is easily induced or modified by the mere presence of anthracene and/or acridine in sufficient amounts. Accordingly, UV photosensitization cannot assure a medicinally acceptable grade of raw material since this characteristic bears only a singular relationship to the total properties of coal tar.

Some manufacturers have incorporated surface-active agents with coal tar and equated their antifungal release activities as a measure of their biological effect (13). Anticipated therapeutic performance, as measured by the reference standard of antiseptic properties, is also unpredictable. Coal tars, regardless of composition, demonstrate considerable fungistatic and bacteriostatic activity. These properties, while of value, have never been demonstrated to be primarily responsible for the clinical efficacy of tar. They are simply additional chemical and therapeutic attributes.

A gas chromatographic procedure is presented for the quality control of crude coal tar, as well as LCD (coal tar solution USP).

[1] Zetar (colloidal whole crude coal tar USP), manufactured by Dermik Laboratories, Inc., Syosset, N. Y.

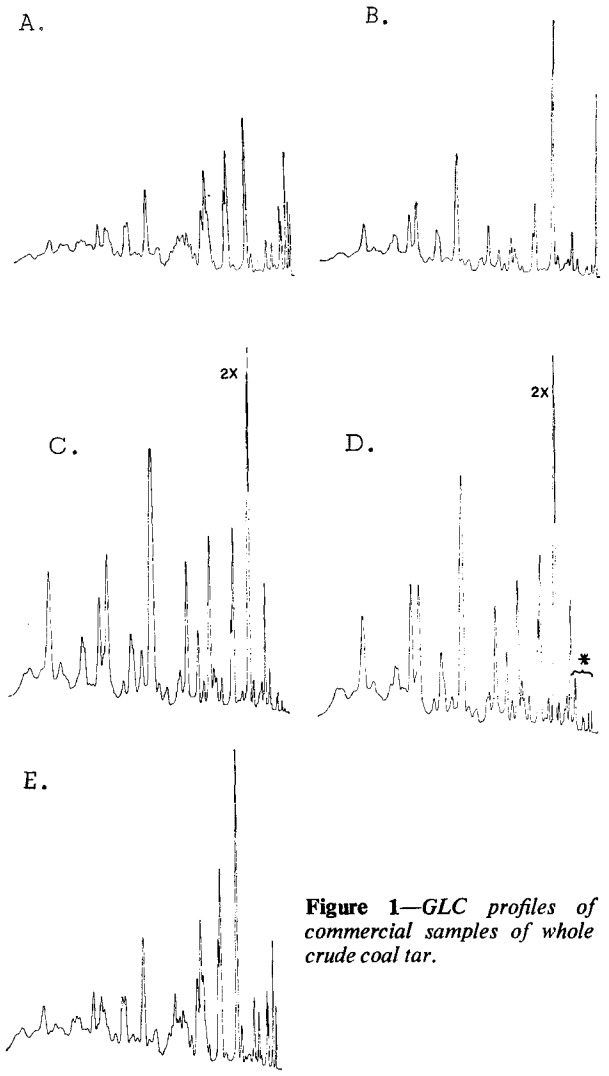


**Figure 1**—*GLC profiles of commercial samples of whole crude coal tar.*

Comparison of the various samples of each indicates the wide and uncontrolled range of presently admissable materials and demonstrates why consistent clinical results are not possible under the present official specifications defining this important topical drug.

The scientific data and information developed would enable the preparation of a monograph, which would exclude from official recognition any coal tar that does not possess comparable physical characteristics and chemical composition.

## EXPERIMENTAL

In order to provide a more selective and specific tar analysis, it was necessary to analyze a number of market samples. These were obtained from various commercial sources and pharmacies, selected at random throughout the U. S. Although all of the samples secured were labeled USP and met present monograph specifications for coal tar and coal tar solution, they did nevertheless demonstrate marked physical differences and profound chemical variations both qualitatively and quantitatively.

**Apparatus**—A dual column Varian Aerograph model 204B chromatograph equipped with dual flame-ionization detectors was employed for all GLC work. Injection port and detector temperatures were 275 and 280°, respectively. Flow rates of 40 ml. He/min., 30 ml. $H_2$/min., and 300-ml. filtered air/min. (supplied by two Oscar's Vibrator Air Pumps) were maintained. Specific parameters are listed for each type of sample and analysis in the sections following.

**Methods and Procedures**—*Crude Coal Tar*—GLC sample size was 0.3 μl. supplied from a Hamilton No. 7101 1-μl. syringe. These

Table I—Solubility and Specific Gravity Data for Illustrated Crude Coal Tar Samples

| Sample | $CS_2$, % Insoluble | $CCl_4$, % Insoluble | Carbenes, % | Benzol, % Insoluble | Sp. Gr.$_{25°}$ |
|---|---|---|---|---|---|
| A | 12.42 | 28.42 | 16.00 | 17.41 | 1.2011 |
| B | 9.64 | 16.89 | 7.25 | 14.22 | 1.2131 |
| C | 3.42 | 9.64 | 6.24 | 6.42 | 1.4232 |
| D | 3.39 | 10.40 | 7.01 | 8.21 | 1.4309 |
| E | 6.71 | 14.02 | 7.31 | 12.19 | 1.2247 |

samples were programmed on a 1.52-m. × 0.32-cm. (5-ft. × 0.125-in.) o.d. stainless steel column packed with 5% SE 30 on 80–100 mesh (chromasorb W, acid washed) from 110 to 255° at 10°/min., and held at the upper limit until no further peaks were recorded.

The variability of the chromatographic portion of crude coal tar was verified using a liquid-solid chromatographic technique on the samples, which involved filling a 22-mm. o.d. chromatographic tube equipped with a stopcock to a depth of 150 mm. with alumina (Grade F-20, Aluminum Corp. of America), and washing with 200 ml. of reagent grade petroleum ether. An accurately weighed 1-g. sample of the crude coal tar was macerated with 5 g. of alumina (prewashed with petroleum ether) and quantitatively transferred to the tube with the aid of 25 ml. of petroleum ether. The sample was eluted using 350 ml. of petroleum ether and the eluate collected at a rate of 4 ml./min. in a tared 400-ml. beaker, evaporated to near dryness on a steam bath under nitrogen, and the remainder of the solvent spontaneously evaporated at room temperature under a stream of nitrogen. The sample was desiccated for 15 min. and weighed. The column was further eluted with 350 ml. of reagent grade ethyl acetate in the same fashion. The residues were in turn run *via* GLC to determine if any significant portion of the petroleum ether eluate was lost in evaporation or any significant amounts of chromatographable material were present in the ethyl acetate fraction.

All other wet tests were performed according to the methods described by de Martin and Cyr (6).

**LCD (Coal Tar Solution USP)**—*Tar Determination*—GLC samples were 2.50 μl. using a Hamilton No. 7105, 5-μl. syringe for injection, programmed from 100 to 255° at 10°/min., and held at the upper limit using the same column as for coal tar. The initial temperature was decreased to allow for better separation of ethanol from the tar constituents. The percent tar was calculated by comparison of peak heights of naphthalene, methyl naphthalene, and phenanthrene *versus* those obtained from a standard using the same crude coal tar diluted to exactly 20.00% w/v in carbon disulfide A.R., according to the calculation:

$$\% \text{ coal tar} = \frac{Ji}{Js} \times \frac{Vs}{Vi} \times Cs \qquad \text{(Eq. 1)}$$

where $Ji$ is the height of peak $j$ in the sample; $Js$ is the height of peak $j$ in the standard; $Vs$ is the injected volume (μl.) of standard; $Vi$ is the injected volume (μl.) of sample; and $Cs$ is the concentration (% w/v) of tar in $CS_2$ used as standard.

*Ethanol Determination*—The column used is 1.52-m. × 0.32-cm. (5-ft. × 0.125-in.) o.d. stainless steel filled with 10% polyethylene glycol[2] on chromasorb W (acid washed) isothermally at 70° with all other parameters as cited previously. The technique involves the use of 20.00% (v/v) acetone A.R./methanol A.R. as internal standard. The height responses were found to be linear between 0.2 μl. and 2.5 μl. of standard. Each analysis is performed using three injections of various volumes between 0.5 and 1.5 μl., both for standard and sample. The ethanol response was plotted *versus* acetone response. Percentage of ethanol is found by determining the appropriate responses for ethanol from the graph in both sample and standard at the same acetone response and employing the following equation:

$$\% \text{ ethanol} = \frac{Ru}{Rs} \times \frac{\text{sp.gr.}_s \times \% Es}{\text{sp.gr.}_u} \qquad \text{(Eq. 2)}$$

where $Ru$ is the response of sample from graph; $Rs$ is the response of standard from graph; sp. gr.$_s$ is the specific gravity of standard ethanol at temperature $T$; sp. gr.$_u$ is the specific gravity of sample at temperature $T$; % $Es$ is the percentage of ethanol w/w in standard; *i.e.*, % $Es$ of 95% ethanol = 92.3. The results were checked according to the USP determination for ethanol as stated in the monograph.

Thirty-five random samples, labeled "crude coal tar USP" of exactly 0.3 μl. each were chromatographed under these conditions; five are presented in Fig. 1 for the purpose of illustration. Samples A and B were obtained from pharmacies, C is representative of material used by these laboratories, and D and E are samples from different batches obtained from another pharmaceutical manufacturer.

[2] Carbowax 20M, Union Carbide Corp., New York, N. Y.

Table II—Comparison of Liquid *vs.* Gas Chromatography for the Determination of Chromatographic Portion of Crude Coal Tar

| Sample | % Chromatographic *via* GLC | | % Chromatographic *via* Liquid Chromatography |
|---|---|---|---|
| | *vs.* Phenanthrene | *vs.* Naphthalene | |
| A | 12.1 | 12.4 | 13.2 |
| B | 17.4 | 17.0 | 15.9 |
| C | 26.2 | 26.9 | 25.8 |
| D | 27.1 | 27.0 | 27.4 |
| E | 21.1 | 20.8 | 20.2 |

## RESULTS AND DISCUSSION

The discrepancies found among the random samples of coal tar USP, both qualitatively and quantitatively, are enormous. The solubility and specific gravity data presented in Table I corroborate the observations of de Martin and Cyr (6); although in the case of Samples D and E, no positive prediction as to formulation compatibility could be made from the data obtained in wet tests. Predictions based on chromatographic evidence were subsequently substantiated by experimental incorporation into washable and greasy bases.

Crude coal tars A, B, and E yielded coarsely dispersed, inelegant pharmaceuticals. Even crude tar received from the same supplier may vary markedly from lot to lot, yielding different GLC profiles and producing visible physical variations in finished products while conforming to USP specifications. The preparations containing material from Samples A through E were not evaluated clinically. However, clinical trials previously conducted demonstrated that different tars produce significantly different patient responses on treatment of various dermatological conditions.

The evident chromatographic differences were checked on a weight basis by GLC and column chromatography to determine the validity of the measurement technique employed. These results are presented in Table II.

The petroleum ether fraction obtained by column chromatography indicated significant losses of benzene, toluene, xylenes, and pyridine. These, however, comprise less than 5% of the chromatographable portion taken on an area response basis; the overall net loss was considered insignificant. More important, excluding the peaks for xylenes, pyridine, benzene, and toluene (starred peaks in Fig. 1), the chromatographic traces were virtually identical to those obtained from the original samples of crude tar. Quantitative measurements based on naphthalene and phenanthrene responses, when compared to the original, yielded results which approximated those found on a weight basis (Table II). No significant amounts of chromatographable material were evident in the trace of the ethyl acetate fractions. Modifications of this technique are being used in this laboratory as a separation procedure for estimating the quality and quantity of coal tar in various preparations. It is obvious that additional separations must be performed if significant amounts of nonpolar materials, such as mineral oil, are present in the finished formulation. However, for this investigation, it did serve to provide additional quantitative evidence of the extent of composite differences which might be expected.

**LCD**—Exactly 2.50 μl. of each of the five samples of coal tar solution (Fig. 2) were chromatographed under the conditions described. Because of the large amount of ethanol present, it was anticipated that the sample size would be inconsistent. Included in

**Table III**—Reproducibility of Peak Heights for LCD Samples (Sample C, Fig. 2)

| Peak | Height, mm. Run 1 | Height, mm. Run 2 | Reproducibility[a] |
|---|---|---|---|
| a | 110.0 | 109.0 | ±0.5% |
| b | 29.8 | 33.5 | ±5.5% |
| c | 33.0 | 34.5 | ±1.4% |
| d | 31.0 | 32.0 | ±1.6% |
| e | 163.2 | 165.5 | ±0.6% |
| f | 67.0 | 65.5 | ±1.1% |
| g | 45.8 | 44.8 | ±1.2% |
| h | 35.0 | 38.6 | ±4.4% |

[a] $\bar{X}$ = ±1.6%.

Fig. 2 are replicate runs of Sample C with peaks labeled "a" through "h." Height ratios were taken as a function of Run 2 *versus* Run 1. These data are presented in Table III and indicate an average error of ±1.6%, which was found to be typical and acceptable.

Each of these samples fulfilled the requirement for coal tar solution as directed in USP XVII (*i.e.*, ethanol content between 81% and 86%). Although no quantitation of the coal tar content of these solutions was attempted, inasmuch as the original tar samples were not available, two coal tar solutions were prepared in the laboratory according to the USP procedure using one randomly selected tar sample. Analyses were performed *versus* the original tar diluted to exactly 20.00% w/v in $CS_2$ *via* GLC using the conditions noted previously. Peaks A, B, and C (naphthalene, methyl naphthalene, and phenanthrene) were used for calculation. The chromatograms are shown in Fig. 3 and the data presented in Table IV. Sample I was estimated to contain 20.29% w/v chromatographable tar and Sample II, 20.46% w/v tar.

Some variations were noted, particularly that the results derived from the phenanthrene peak produced lower, although acceptable, results than either of the other two employed. The authors' suspect that some sorption of phenanthrene occurs on the sand and, from the data, it appears to be approximately 6.5% of the amount present. Since a detailed investigation was not performed regarding this possibility, the authors chose to include no correction and the results are presented as a mean of the determinations from each of the three selected peaks. On an overall basis, no significant sorption of the chromatographable portion of the tar is apparent, thereby presenting a much more valid assay procedure for coal tar solution USP (LCD).

It is important to emphasize that *none of the LCD and "extract" samples actually contain the labeled amount of coal tar (20%).* This figure (20%) is based on the amount of crude coal tar initially added to the ethanol, sand, and polysorbate 80, and not the amount of coal tar remaining in the extract after filtration. For example, Sample I of LCD was analyzed for water content *via* the classical Karl Fischer method and found to contain 6.5%. Combined with the ethanol data (81.39% per USP analysis), this leaves a material balance of 12.1% of which 5.0% is polysorbate 80. (The polysorbate 80 does not, for all practical purposes, ab(ad)sorb on the sand used in the laboratory preparation of LCD.) This leaves *approximately 7% tar "fractions" in the LCD solution*, the bulk of which is chromatographable.

Previous clinical research by Obermayer (9) has demonstrated that no particular fraction or fractions derived from whole crude coal tar yield total clinical results comparable to whole crude coal tar. In fact, certain of the fractions he tested had little or no medicinal value. It is quite evident, therefore, that even a "standardized" LCD constitutes only a fraction of the total composition of crude coal tar and cannot be considered a 20% solution. It similarly cannot be expected to produce comparable and reproducible therapeutic results.

Finally, a check of a simple GLC technique for the determination of ethanol was performed to assure the validity of the findings. Each of the samples was analyzed in duplicate and confirmed by the USP distillation procedure. These data were presented in Table V. All were found to conform, as stated previously, to the USP monograph for coal tar solution (LCD).

As an alternate to polyethylene glycols,[2] the authors have used a column of 1.52-m. × 0.32-cm. (5-ft. × 0.125-in.) o.d. stainless steel, filled with Poropak Q, isothermally at 150° with some success. However, this column becomes inconvenient when several samples of coal tar solution are to be analyzed since the elution of portions of the tar interferes with subsequent injections. Clearing of the column overnight at elevated temperatures was not always sufficient. Since no problem of this type was found with the polyethylene glycols[2] column (overnight purging at 195° was sufficient to clear it of retained chromatographable tar components), this is the column of choice for this procedure.

## CONCLUSIONS AND SUMMARY

From the data reported in the literature regarding whole crude coal tar and LCD, certain differences were expected due to the variability of source, conditions of distillation, and modes of collection used in the manufacture of coal tar. This investigation has demonstrated that the situation is far more critical than originally suspected. The combination of previously discussed factors has resulted in an incompletely controlled drug and the indiscriminate manufacture of crude coal tar substitutes which include fractionated

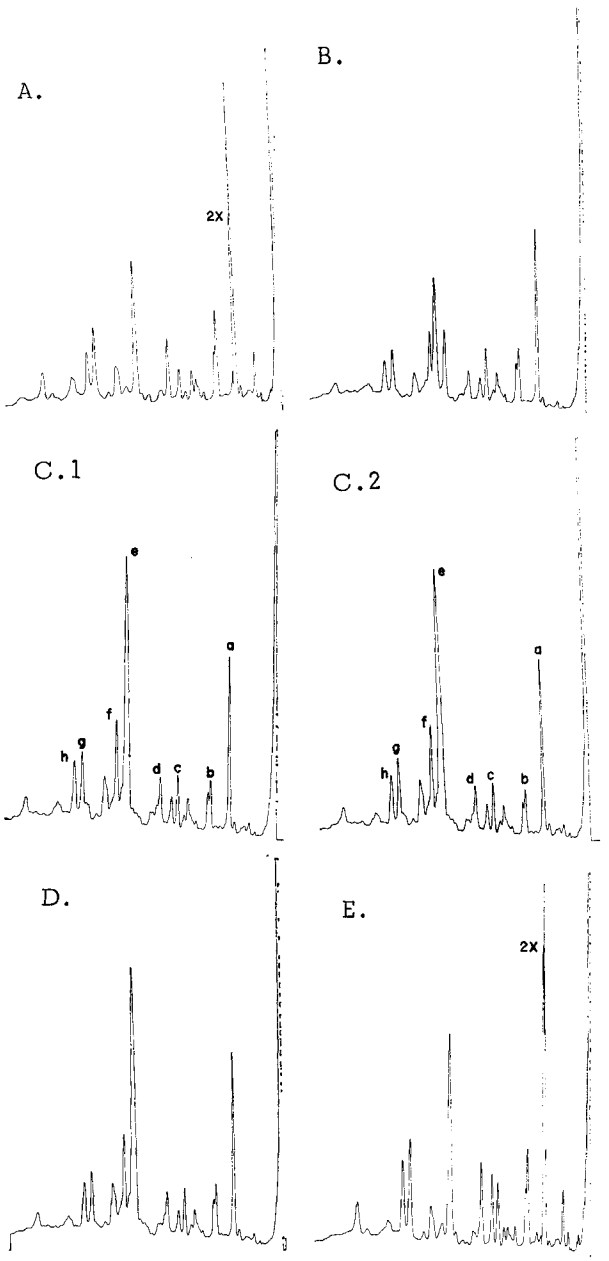


**Figure 2**—*GLC profiles of commercial samples of LCD.*

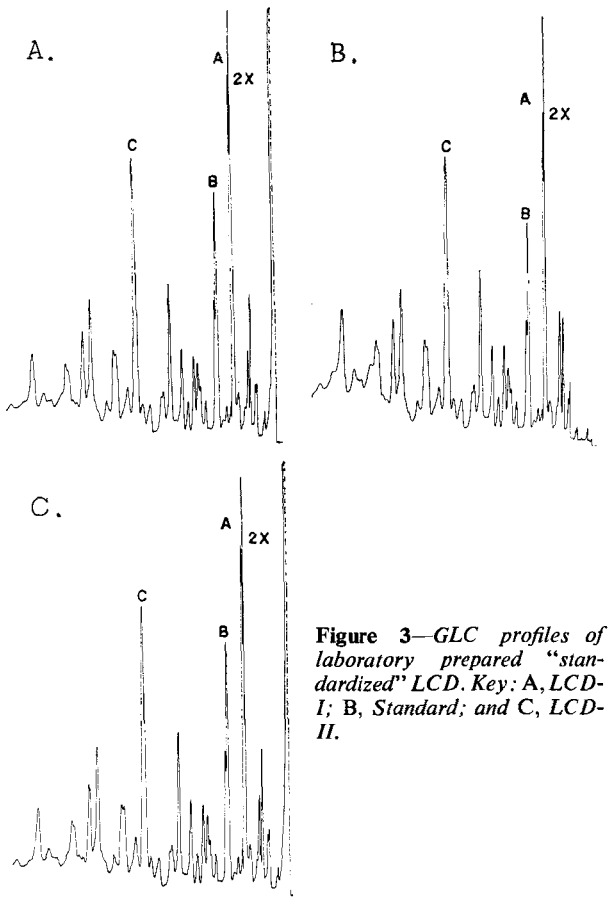


**Figure 3**—*GLC profiles of laboratory prepared "standardized" LCD. Key:* A, *LCD-I;* B, *Standard; and* C, *LCD-II.*

extracted, filtered, and synthesized liquids, which bear little physical and chemical resemblance or correlation to a therapeutically acceptable grade of crude coal tar.

The authors have presented a new approach to the chemical standardization and analysis of this drug. In addition, an alternate method for determining the ethanol content of coal tar solution USP (LCD) is presented, which is equivalent to, and more rapid than, the procedure specified in the pharmacopeia.

It is reasonable to conclude that by designation of starting raw material, shape and size of retort, destructive distillation temperature, temperature during tar collection, and various other factors, in conjunction with laboratory specifications (including 15% maximum permissible variation in any one of the selected major constituents of the chromatographable portion of the tar, with differential solubility and specific gravity data), one would produce a tar demonstrating little or no inconsistencies in composition from batch to batch. In fact, this GLC technique has been routinely and successfully employed in the authors' laboratory for the past 2 years. It is equally obvious that while GLC standardized crude coal tar may yield a "standardized" LCD, the activity of this or any other "extract" cannot be expected to approach the efficacy obtained from the original whole substance.

This investigation is intended as a beginning, and further research pertaining to a nonchromatographable fraction of crude coal tar, as well as the sorption phenomena which occur in the manufacture of coal tar solutions, is being conducted. Additional analytical methods such as wet analyses and differential solubilities are being explored. These further investigations present interesting possibilities for future reports.

**Table IV**—Analysis of Laboratory Prepared LCD

| Standard | | LCD I[a] | | LCD II[b] | |
|---|---|---|---|---|---|
| $V_s$ = 2.32 μl. | | $V_i$ = 2.49 μl. | | $V_i$ = 2.51 μl. | |
| Peak | *Js* | *Ji* | % Tar | *Ji* | % Tar |
| A | 76.2 | 85.19 | 20.84 | 83.11 | 20.16 |
| B | 51.3 | 59.10 | 21.47 | 60.10 | 21.98 |
| C | 66.1 | 67.10 | 18.92 | 68.71 | 19.21 |

[a] $\bar{X}$ = 20.41%. Est. = 20.29%. [b] $\bar{X}$ = 20.45 %. Est. = 20.46%.

**Table V**—Comparison of GLC *vs.* Distillation (USP) Method for the Determination of Ethanol in LCD

| Sample | % $C_2H_5OH$ (USP) | % $C_2H_5OH$(GLC) |
|---|---|---|
| A | 83.70, 83.61 | 83.40 |
| B | 85.43, 85.59 | 85.72 |
| C | 82.10, 81.89 | 82.06 |
| D | 84.20, 83.96 | 83.82 |
| E | 81.69, 81.88 | 81.80 |
| I[a] | 81.42, 81.36 | 81.10 |
| II[a] | 81.30, 81.56 | 81.15 |

[a] Laboratory preparations.

Since whole crude coal tar is not a chemical entity and its total therapeutic effect is dependent upon a myriad of carbonized and volatile constituents, achievement of complete and absolute uniformity of clinical results is improbable. It is apparent, however, that modern, precise analytical instrumentation can be utilized to revise the inadequate USP monograph on coal tar. A GLC tar profile, together with adequate chemical and physical specifications, will assure pharmacists of minimum rather than maximum variations in composition. Consequently, physicians may anticipate greater consistency and uniformity of therapeutic results.

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