ACUTE HEPATIC PORPHYRIA AND PSYCHOSES¹
(Experience of twelve years)

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SUMMARY

A sample of 805 psychotic patients belonging to different groups was screened for acute hepatic porphyria during 1975 to 1987 by observing urinary colour change on standing to brown red colour and for positive Watson-Schwartz test, indicating increase in urinary porphobilinogen which is diagnostic of acute hepatic porphyria. 27.95% cases had shown positivity which was further confirmed by quantitative estimation using spectrophotometric method of Rimington. However, when these positive cases were subjected to more specific tests viz, additional butanol extraction modification to Watson-Schwartz test and quantitative estimation of porphobilinogen by ion-exchange resin column chromatographic method of Mauzerall & Grannick, only 1.12% could confirm their positivity. These cases were only, diagnosed as acute hepatic porphyria. The positivity to the non specific, yet accepted diagnostic tests for acute porphyria observed in remaining 26.8% psychotics was an amazing unexplained phenomenon. It was suggestive of the presence of a non specific porphyrin activity.

Acute porphyria amongst psychotics was first described by Waldenstrom (1937). He got most of his cases by a routine survey of urine from patients in Swedish mental hospital (Kark, 1955). Goldberg (1959) in a study of 50 cases of acute porphyria reported six cases who could be legally certified as insane; nine cases found to be confused, hallucinated and disoriented and another 14 who were depressed and behaving peculiarly. Mecalpine and Hunter (1966) on the basis of retrospective account of urinary colour change concluded that insanity of King George III, which could be manic depressive psychosis, was due to acute porphyria. There are many other workers, who had also reported acute porphyria in psychotics (Saint et al., 1954; Peters et al., 1958; Roth et al., 1968; Stein & Techudy, 1970). Thus, we find that there exist a definite association of hepatic porphyria with psychoses. However, the extent of this relationship, and how porphyria causes psychoses is still ill understood. The author came across a significantly high number of psychotics, during three screening studies (Golechha, 1977; Golechha et al., 1981 & 1985). The paper presents authors experience of finding acute porphyria in psychiatric practice specially amongst psychotics studied during last twelve years and discusses the problem of biochemical diagnosis and various advances made in the field.

MATERIAL

Total of 805 psychotic patients from 1975 to July 1987 were examined for evidence of acute porphyria. 689 of them formed the part of screening studies for porphyria during 1975 to 1981. Another 116 cases of psychoses belonging to high suspicion group for acute porphyria were also screened. The criteria of high suspicion for acute porphyria are given in appendix 'A'. It was evolved on the basis of the experience gathered in the preceding years. These age ranged from 10 to 55 years with mean age of 25.8 years. Male female ratio was 2.77 : 1.

Cases in group A, were consecutively admitted new cases or first seen in OPD irrespective of age, sex and diagnostic sub category. The diagnosis was based on ICD-9. A matched control of 562 healthy volunteers was also screened for better standardization of results.

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### TABLE I. Test sample sub groups, source and number of psychotic patients

| Group | Year of study | Place | Total No. of psychiatric patients screened for porphyria | Number of psychotic patients |
|-------|---------------|-------|--------------------------------------------------------|-----------------------------|
| A—1975 | Military Hospital, Jhansi | 1978 | 107* | 19 |
| 1978 | KGMC Lucknow & Command Hospital, Lucknow | 1979 to 1981 | 519** | 305 |
| 1979 to 1981 | Command Hospital, Lucknow | 890*** | 965 |
| Total | | | 1516 | 689 |
| B—1982 to 1987 | Psychotics with high suspicion of acute porphyria studied at Tezpur & Delhi | | | 116 |
| Total Psychotics | | | | 805 |

*Golechha G. R., 1977; **Golechha et al., 1981; ***Golechha et al., 1985.

### METHODOLOGY

All patients were clinically evaluated in detail. Cases found positive for porphobilinogen were periodically followed up for urinary excretion of porphobilinogen.

**A. Sample collection:** Freshly voided urine was collected in clean colourless glass containers. The time of collection was random. Mostly it was at the time of first examination on attending the OPD or on admission before any treatment was commenced. In about 153 cases it was not possible as the patients were not co-operative and were violent. They were tested on subsequent days. In three cases catheter sample was obtained as patients were in stupor and bladder was distended. Seven cases supplied plain water instead of urine for reasons best known to them.

**B. Qualitative estimation of porphobilinogen:** This was done by Watson-Schwartz Test (Watson & Schwartz, 1941; Varley & Gowenlock, 1980) with modification of butanol extraction in stages (Watson et al., 1961 & 1964). A portable kit was used for immediate testing of urine on voiding. An acid control was run parallel with each test sample to detect any false positive result. The chloroform extractions were repeated till no further colour was extracted. Tests were repeated during follow-up in positive cases.

**C. Quantitative estimation for porphobilinogen:** It was done in all Watson-Schwartz Test (W. S. test) positive cases by methods of Rimington (1958, 1961) within 2 to 3 hours on the same samples on which W. S. test was already performed. Column chromatographic estimations by method of Mauzerall & Grannick's (1956) as modified by Marvar et al. (1966) were carried out in a representative samples which were drawn from 3 different groups, positive for Modified W. S. test (M. W. S. test), only Original W. S. Test (O. W. S. test) positive and W. S. test negative groups. This was for comparison of findings obtained by Rimington's method and to know the difference of values between M. W. S. test positive & only O. W. S. test, positive samples.

**D. Colour change of urine on standing:** Urine samples were exposed to sunlight in colourless glass containers for 2 to 7 days depending on weather and duration of sunlight. Any change of colour to brown red i.e. port wine or brown red with blackish hue i.e. cococola colour was noted.

**E. Fluorescence test:** Urine and faeces were seen in ultra violet light using Wood's lamp or red fluorescence to find uro & copro
porphyrins as described by Rimington (1958).

**F. Clinical evaluation**: It was made in all cases. History in detail including onset, presence of precipitating factors, past episodes any significant past and family history and history of drugs taken during past 24 hours of urine testing and during previous 7 days were recorded. Detailed physical and mental status examination was done. Family pedigree of some of the positive cases were worked up.

**G. Follow-up study**: Follow-up testing of urine for W. S. test and quantitative estimation of porphobilinogen was done once a week in positive cases for 4 to 6 weeks.

There were 82 cases of organic psychoses and 723 cases of functional psychoses, ratio

| Diagnosis                          | W. S. test positive | M. W. S. positive |
|------------------------------------|---------------------|-------------------|
|                                    | Number of cases     | %                 | Number of cases | %     |
| **A—Test sample**                  |                     |                   |                 |       |
| ICD-9                              |                     |                   |                 |       |
| 290.4 Arteriosclerotic Dementia (N=1) | 1                   | —                 | —               | —     |
| 291 Alcoholic Psychosis (N=12)     | 2                   | 16.6              | —               | —     |
| 292 Transient Organic              |                     |                   |                 |       |
| Psychotic Condition (N=44)         | 10                  | 22.7              | 3               | 6.8   |
| 294 Other Organic Psychotic Condition (N=25) | 8                  | 32.0              | 3               | 12.0  |
| 295 Schizophrenia (N=505)          | 148                 | 29.3              | 3               | 0.59  |
| 296.0 Mania & Hypomania (N=110)    | 28                  | 25.4              | —               | —     |
| 296.1 Depression (N=66)            | 23                  | 26.7              | —               | —     |
| 297 Paranoid States (N=15)         | 3                   | 20.0              | —               | —     |
| 298 Acute Paranoid Reaction (N=7)  | 2                   | 28.5              | —               | —     |
| **Total (N=805)**                  | 225                 | 27.95             | 9               | 1.12  |
| **B—Control**                      |                     |                   |                 |       |
| Matched control of group B & C     | 562                 | 3.1               | —               | —     |

**Table III. Urine colour change on standing & W. S. test positivity**

| Diagnosis                          | No. of cases showing significant colour change | No. of W. S. test @ positive cases | No. of cases positive for M. W. S. test |
|------------------------------------|-----------------------------------------------|-----------------------------------|----------------------------------------|
| Alcoholic Psychosis (N=8)          | 2                                             | 1                                 | —                                      |
| Transient Organic Psychosis (N=28) | 14                                            | 9                                 | 3                                      |
| Other Organic Psychosis (N=18)     | 5                                             | 4                                 | 2                                      |
| Schizophrenia (N=291)              | 114                                           | 101                               | 2                                      |
| Mania & Hypomania (N=69)           | 24                                            | 19                                | —                                      |
| Depression (N=58)                  | 20                                            | 17                                | —                                      |
| Paranoid States (N=12)             | 3                                             | 3                                 | —                                      |
| Acute Paranoid Reaction (N=8)      | 2                                             | 1                                 | —                                      |
| **Total N=500**                    | 184(36.8)                                     | 155(31)                           | 7                                      |

@ It includes (O. W. S.)—M. W. S. test positive cases.
### Table IV. Groupwise positivity W. S. test

| Study group | M. W. S. test positive | Only O. W. S. test positive | Total W. S. test positive |
|-------------|------------------------|----------------------------|--------------------------|
|             | (Butanol modification) |                           |                          |
| I. Screening study |                        |                            |                          |
| Group A     | N=689                  |                            |                          |
|             | N                      | %                          | N                        |
|             | 7                      | 1.02                       | 163                      |
| II. High suspicion criteria cases |                |                            |                          |
| Group B     | N=116                  |                            |                          |
|             | 2                      | 1.72                       | 58                       |
| Total Group | A+B                    |                            |                          |
|             | N=805                  |                            |                          |
|             | 9                      | 1.12                       | 216                      |

### Table V. Follow-up estimation PBG by Rimington's method (W. S. test positive cases)

| Diagnosis            | No.  | Initial values of PBG | PBG values after 4 weeks |
|----------------------|------|------------------------|----------------------------|
|                      |      | Mean | SD | Mean | SD |
| Schizophrenia        | 42   | 3.1  | 3.96 | 2.3  | 1.3 |
| Mania & Hypomania    | 12   | 7.3  | 2.03 | 2.8  | 1.5 |
| Depression           | 9    | 7.6  | 2.78 | 3.1  | .87 |
| Organic Psychoses    | 4    | 7.2  | 2.1  | 2.4  | 1.05 |
| Total                | 67   | 7.83 | 2.71 | 2.44 | 1.2 |

p < .001

### Table VI. Comparison of porphobilinogen values estimated by the two different methods

| Samples | Rimington's method | Column chromatography @ |
|---------|---------------------|-------------------------|
|         | PBG/Litre           | PBG mgm/Lit. | ALA mgm/Lit. | AA mgm/Lit. |
| (a) O. W. S. positive (N=11) |                      |                    |
| Mean    | 8.04                | .91                | 1.5           | 4.5          |
| Sd      | 1.22                | .77                | .6            | 1.01         |
| (b) M. W. S. positive (N=2) |                      |                    |
| 1.      | 28.05               | 20.07              | 3.20          | 5.08         |
| 2.      | 30.05               | 21.9               | 3.5           | 2.56         |
| (c) O. W. S. negative (N=2) |                      |                    |
| 1.      | 2.3                 | .54                | .44           | 2.56         |
| 2.      | 1.24                | .07                | .1            | 2.94         |

@ Method of Mauzerall & Grannick's (1956) as modified by Marvar (1966).
Statistical evaluation for porphobilinogen value in group (a) by two methods reveals—t = 16.27, p < .001, r = .04.
being 1 : 8. 8. Schizophrenia formed the bulk of it (62.7%) followed by mania & hypomania (14.9%), depression 10.7% & transient organic psychoses 5.5%. O. W. S. test was found positive in 27.95% of the total sample as shown in Table I as compared to 3.1% test positive in matched control of healthy volunteers (p<.001). Out of these only 9 cases had given positive result with butanol extraction modification of W. S. test forming 1.12%.

Diagnostic category of psychotics showing W. S. test positive is shown in Table II. Cases showing urinary colour change on standing is shown in Table III.

Out of 500 cases belonging to both organic and functional psychoses 36.8% had shown significant colour change of urine on standing which varied from port wine to brown red with blackish hue i.e. cococola colour over 7 days time. In seven cases colour development was so intense that it appeared black. There was no difference of colour in modified W. S. test positive and those negative for butanol modification but positive for only original W. S. test. In 5.8% of cases colour change was noticed but W. S. test were negative. The colour change was found to occur faster in summer and bright sunlight.

Cases selected after application of high suspicion criteria for acute porphyria, as seen in group D in Table IV had shown significant increase in detection of cases of positive Watson-Schwartz test of both types.

Quantitative estimation by Rimington's methods: Cases showing only original W. S. test positive were found to have porphobilinogen by Rimington's method ranging from 4 mgm to 18 mgm per litre. Mean being 9.4 mg/Litre SD =2.8. In M. W. S. test positive samples it ranged from 10 mg to 30 mg/Litre. Mean being 19.5 mg/Litre SD = 7.3. No significant difference in the values could be found disease wise, but three cases of stupor two of which were catatonic and one depression had shown only O. W. S. test positive with surprisingly high value of 15 to 18 mg/Litre. The urine was obtained through catheter and tested immediately for W. S. test. The laboratory follow-up of 67 cases after 4 weeks (Table V) had shown reduction in porphobilinogen values by this method. The W. S. test was negative at this time and there were no colour change in urine on standing except late development in 9 cases. The patient had shown improvement in their clinical condition.

Column chromatographic estimation of porphobilinogen (PBG), Aminoeyulilic acid (ALA) and Amine acetone (AA) was done in 11 original W. S. test positive samples which were negative for modified test, 2 modified test positive and 2 W. S. test positive urine samples which is shown in Table VI. PBG values by Rimington's method estimated simultaneously are also shown for comparison.

PBG estimated by Rimington's method is much higher than that estimated by column chromatography in O. W. S. positive group. Whereas in M. W. S. positive group it correlates better by two methods.

Ultraviolet fluorescence tests: Results were in conclusive due to absence of strong fluorescence and unfamiliarity with the test. It did not contribute to the study.

Clinical evaluation: Analysis of clinical evaluation in O. W. S. positive and M. W. S. positive cases reveal no difference. Positivity of butanol modification has no bearing on clinical course except that it was found more positive (7.3%) in organic psychotic condition than in schizophrenia (.59%). Out of six organic psychoses cases where M. W. S. test was positive two cases presented with fleeting neurological symptoms without any fixed neurological deficit. They had history of pain in abdomen and severe constipation before the onset of delirium. Third case was a male muslim mess waiter who was examined for his "drunken behaviour" without having taken alcohol or any drug.
He was thought to be a case of acute demyelinating syndrome by treating physician. He was referred for his associated behavioural abnormality. Fever, exhaustion and reduced calory intake were the probable precipitating factors. Fourth case was of seizure who had no relief with phenobarbitone & dilantin sodium and developed psychotics episode of schizophrenic type and complained of abdominal pain. Remaining two cases were diagnosed encephalitis. They were referred for management as they became violent and aggressive in medical ward. History revealed that they were given a course of antimalarial for the febrile illness without any proof of malaria and were delerious. The three cases of schizophrenia who had positive M.W.S. test gave history of pain in abdomen. They exhibited the delusion of being poisoned and had hallucinations, passivity and persecution more prominent.

In the O.W.S. positive group there were seven cases belonging to transient organic psychosis. They presented with toxic confusional state of unknown etiology. Precipitation by drugs was found in 6 cases, in 3 due to barbiturate, in one due to sulphur and other two by chloroquine and other antimalarial. Five cases with other psychotic condition included epileptic psychosis, Encephalitis and metabolic encephalopathy, who were referred for their abnormal behaviour. Curiously one case was of hypothalamic syndrome who had shown partial improvement without any specific treatment. The largest number of O.W.S. positive test cases were of schizophrenia. About 70% of these cases had acute onset, hallucinatory behaviour and complained of somatic symptoms viz aches or pain, abdominal and non abdominal. About 40% had catatonic features. Passivity and persecutory ideas were present in 50% of them. 30% had belief of having been given something to eat in the food or thought that they are being poisoned. All of these cases had shown evidence of autonomic neuropathy. Eight percent had shown presence of one or more precipitating factor as listed in appendix.

**Drug history**: It revealed about 479 cases in test sample of 805 had taken/been given some or other drugs during past 7 days. Only 300 had taken drugs during last 24 hours before examination/testing. Details of drug could not be established in about 200 cases. Phenothiazine and butyrophenone group of drugs were taken by 216, benzodiazipine in 200 and antidepressants in 86 cases. Many patients had more than one drug. There were more test negative results in patients receiving phenothiazine and other psychotropic drugs than in those who did not take them. Ratio of positivity was 1:1.9.

**Family screening**: No history of diagnosed case of porphyria could be found in any of our positive M.S.W. or O.W.S. cases. 37 cases gave history of psychotic disorder in their first degree relatives. Family history of neurological disorders i.e. paralysis and seizure were found in 13 cases and recurring pain abdomen in 19 cases. 69 first degree relations of 13 positive O.W.S. and 2 positive M.S.W. cases were screened by Rimington's method. Only O.S.W. test was found +ve in 37 of them. Modified W.S. test was negative in all of them. Even 7 relation of the two M.W.S. positive cases had shown only O.W.S. test positive. All of them were asymptomatic and had no history of any past episode.

**Amino Acetone**: Table VI shows high values of amino acetone in urine of O.W.S. positive psychotics as compared to normals and values of porphobilinogen found in their own urine by column chromatography. Role of Amino Acetone, an aminoketone, in biological fluids is still not well understood and needs further research (Marvar et al., 1966).
DISCUSSION

Mental changes are an important manifestations of acute porphyria and have been described by Markovitz in U. S. A. (1954), Waldenstrom in Sweden (1957), Goldberg in U. K. (1959) and Eales in S. Africa (1962) varying from 50 to 80%, in their patients of acute porphyria. Kaelbling et al. (1961) had reported 35 positive cases amongst psychiatric patients screened in Ohio. Ten had schizophrenia, two had psychotic depression and ten cases were diagnosed as acute or chronic brain syndrome. They concluded that psychiatric disorder may be the only manifestation of porphyria. Peters et al. (1958) described porphyric schizophrenic syndrome when they found positive Watson-Schwartz test in the urine of schizophrenics. The evidence of porphyric activity in psychotics was further established by the work of Peter et al. (1985) when they found diminished PBG deaminase activity in the erythrocytes of 70 individuals forming 1.8% of the total sample from 2 psychiatric hospitals in U. S. A. But in their final analysis they diagnosed only .21% as cases of acute porphyria on the basis of increased PBG by Mauzerall & Grannick's method.

In this 12 years study if we exclude the high suspicion group, then psychotic forms 45.45% of total psychiatric patients population of 1516 who were screened, out of which 1.02% could be diagnosed as cases of acute porphyria as their modified W.S. test was positive and quantitative estimation of true porphobilinogen was also high as found by column chromatographic method of Mauzerall & Grannick, modified by Marvar (1966). On the same testing criteria this percentage increased to 1.7% in group D where we adopted high suspicion criteria for acute porphyria in selecting the case for porphyria testing. What is more astonishing is that the group of only original W.S. test positive cases which formed 23.7% of our test sample of psychotics. In group D this has risen to 45.7% when high suspicion criteria of selecting cases for acute porphyria testing was adopted. These O.W.S. positive cases could have been accepted as cases of acute porphyria before 1961. When finding too many W. S. test positive cases Watson et al. (1961, 1964) advocated butanol modification to weed out false positive results and emphasis was laid on isolation of porphobilinogen on ion exchange resin and then quantifying it as per the method of Mauzerall & Grannick. As a corollary to these additions very rightly, we find significant decrease in reporting of acute porphyria cases in the world literature. Our study is unique in the sense that we adopted, apart from clinical evaluation, three different objective parameter for finding evidence of porphyria in our patients. The first one was the recording colour change of urine on standing to brown red i.e. port wine colour. Though clumsy and crude test, it was equally useful in a clinical setting to indicate probable evidence of acute porphyria. The colour change occurs due to enzymic and nonenzymic conversion of porphobilinogen into porphobilin and uroporphyrin (Watson & Schwartz, 1941; Waldenstrom, 1957; Dean, 1971; Elder, 1980). There is no large scale study which has reported on this aspect of porphyria. The second parameter used was original W. S. test done in stages using N. acetate as buffer before the chloroform extraction. An acid control was run parallel with each test. Chloroform extraction was repeated till no further colour could be extracted. The recording of drug history and its relation to test positivity further helped in ruling out the positivity simply on account of drugs (McEwen & Patterson, 1972). Thus false positivity of Watson-Schwartz test was cautiously guarded. The third objective parameter used was quantification of porphobilinogen by spectrophotometric estimation by Rimington's method in all W. S. test positive cases initially, and in some
on follow-up after 4 weeks. In about 30% (67) of O.W.S. positive cases, finding of decreased value of porphobilinogen after treatment for 4 weeks corresponding to clinical recovery of the patient was a significant observation (Table VI). When we look at the column chromatographic estimation of porphobilinogen (Table VI) it becomes very clear that porphobilinogen isolated and estimated by Mauzerall & Grannick's method is that, whose aldehyde compound is insoluble both in chloroform and in butanol as seen in positive modified W. S. test. The fact which is accepted and applauded by part of scientific community (BMJ, 1975). Yet, some authorities (Varley, 1980 and Elder 1980) do not recommend this butanol modification to original W. S. test even after 20 years of its advocacy by Watson et al. (1961, 1964). This proves the grey zones and dilemma of research in this field. Obviously there appears to be more than one biochemical entity which is branded singly as porphobilinogen. This concept is shared by many pioneer workers in this field viz Watson et al. (1961, 1964) and Irvin (1974, 1978). They think that there are some other intermediary products like various porphyrinogens, other monopyrroles i.e. kryptopyrrole and its lactum, different isomers of porphobilinogen, polypyrroles and certain indoles (Ludwing, 1958) which may be responsible in causing the clinical manifestation of disorder and may give positive original Watson-Schwartz test or be negative for butanol extraction. Thus, this concept of the presence of other Ehrlich's aldehyde compounds indicating non specific porphyric activity is an accepted one.

The study shows a close association between psychoses and acute hepatic porphyria. Till further exploration, non specific tests like urinary colour change on standing, original Watson-Schwartz test and quantitative estimation by Rimington's method should be adopted as indicator of porphyria activity without going into biochemical controversy of true stable form of porphobilinogen or transient unstable other Ehrlich's aldehyde reactors, if we do not wish to miss the clinical case material with porphyric activity. Any research on psychoses should include these parameters and others to assess
the extent of porphyrific activity, as they may have contributed to some extent in developing the psychotics process. These tests can also serve objective means to monitor clinical improvement in cases of psychoses and may have predictive values. Entity of acute porphyria must be kept in mind whenever high suspicion criteria as given in appendix are fulfilled, while dealing with psychotics or psychiatric patients in general.

Acknowledgement

I am highly indebted and grateful to Brig S. B. Chatterjee, Professors B. B. Sethi, S. S. Agarwal & A. K. Agarwal without whose encouragement and active co-operation, this study would have remained incomplete. I am highly thankful to Lt. General, Suraj Prakash, Commandant Army Hospital Delhi Cantt. (presently Director General Medical Services, Army) and Air Commodore I. C. Sethi, Consultant Psychiatry for their encouragement and guidance in completion of this study.

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Appendix ‘A’

Criteria for High Suspicion of Acute Porphyria in a Psychotic Patient

History or presence of any one factor from group ‘A’ and two from group ‘B’ in a psychotics was considered to be indicative of high suspicion for Acute Porphyria.

Group A
1. Unexplained recurring abdominal pain—acute colicky, subacute or chronic diffuse and non specific.
2. Unexplained neurological symptoms—paresis, paralysis, paraesthesia and seizures.
3. Precipitation by barbiturates, sulphas, chloroquine and other antimalarials.
4. Past and family history of porphyria.
5. Passing of red coloured urine (with no lab evidence of blood) or urine changing to brown red colour on standing.
6. Unexplained altered level of consciousness including stupor.

Group B
1. Acute onset (up to seven days).
2. Unexplained non abdominal pains and aches.
3. Skin lesions—photosensitivity, pigmentation, burning, stinging, urticarial swellings, bullae and blisters.
4. Evidence of autonomic neuropathy by any two of the follow Tachycardia (Pulse > 90/mt) or Bradicardia (Pulse < 60/mt) Hypertension—B. P. systolics > 150 mm, diastolics > 90 mm, Constipation > 72 hours. Unexplained diarrhoea or vomitings. Unexplained giddiness.
5. Precipitation by any two—exhaustion, starvation, infection, fever, trauma (surgical or non surgical) menstruation or pregnancy in females. Drugs other than listed in group A e.g. contraceptive pills, Isonex, Griseoflavine or others known to have porphyrogenic activity.