One infant was microcephalic, and both infants showed delay in motor development. The C.S.F. protein was increased in both cases, but the fits which occurred in the first two days of life in Case 1 may have been due to hypoglycaemia. An episode of collapse and loss of consciousness in this infant at 2½ months of age was associated with a bulging fontanelle and high C.S.F. protein. Virus was not isolated from the C.S.F. as it has been in some cases (Korones *et al.*, 1965).

Eye defects were found in both cases. In Case 1 cataract, corneal oedema, and buphthalmos were present, and in Case 2 the cataracts were not apparent until 4 weeks of age. Development of cataracts after birth has been reported by Banatvala *et al.* (1965). Deafness was detected in Case 2.

The persistence of rubella neutralizing antibody was demonstrated in both infants. In Case 1 serum taken on the second day of life had an antibody titre of 4, which was much lower than the mother's (128). This finding may represent rapid elimination of maternal antibody due to virus infection in the infant (Soothill, personal communication, 1965). Subsequent antibody titres in the child's serum at 3, 4, 6, and 9 months of age were 32, 32, 64, and 64 respectively. Unfortunately, owing to a shortage of serum, it was not possible to repeat the test on the first specimen of serum to determine whether there was in fact a significant rise in titre between the initial and subsequent sera, the latter being tested together. Apart from this possible rise in titre, active immunity was indicated by the persistence of antibody to the age of 9 months, by which time passively transferred maternal antibody is unlikely to be detected. In Case 2 antibody persisted in the infant's serum from 3 to 6 months of age, again confirming active rather than passive immunity.

Estimation of immunoglobulin levels showed that both infants had high levels of IgM for their ages. This confirms by a quantitative method the findings of Alford (1965) and of Bellanti *et al.* (1965), who used the qualitative technique of immunoelectrophoresis. IgG levels were relatively high in Case 1 at 8 months and in Case 2 at 6 months of age. The absence of IgA in Case 2 at 6 months may be abnormal for her age, but further follow-up is required. In both cases it is probable that the elevated IgM was due to the antigenic stimulus of rubella virus, but the presence of liver disease must be regarded as a possible factor (Soothill, personal communication, 1965).

The infectiousness of congenital rubella is illustrated by both cases, as several contacts developed rubella. The period of virus excretion was found to be three months in Case 1 and at least eight months in Case 2. It may occasionally be as long as nine months (Lambert *et al.*, 1965). This presents a problem in providing the necessary isolation facilities during the prolonged period of hospitalization that may be necessary, and in avoiding contact with anyone in the early months of pregnancy.

Summary

The clinical features, virus studies, and quantitative immunoglobulin estimations in two cases of congenital rubella occurring in England are reported. There was no history of an illness or of contact with rubella during the pregnancies. Both infants had clinical evidence of systemic disease; rubella virus was isolated in one case from the nasopharyngeal swabs and urine, and in the other case from nasopharyngeal and conjunctival swabs, lens material, and a biopsy specimen of liver, which was only slightly abnormal on microscopy. Virus excretion persisted for several months, and cases of rubella occurred in personnel caring for each patient. There was evidence of active immunity to rubella, and both infants had high levels of IgM.

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Requests for reprints should be sent to Dr. W. C. Marshall.

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Urinary Excretion of Porphyrin Precursors and Coproporphyrin in Healthy Females on Oral Contraceptives

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Oestrogenic compounds or combinations of oestrogenic and synthetic progestational agents are known to cause frequently an increased excretion of the porphyrin precursors δ-aminolaevulic acid (ALA) and porphobilinogen (PBG) in patients suffering from acute intermittent porphyria. Less frequently, however, they cause clinical exacerbation of acute intermittent porphyria (Redeker, 1963; Welland *et al.*, 1964; Wetterberg, 1964), and may even prevent the symptoms of acute intermittent porphyria, as happened in the case mentioned by Haeger-Aronsen (1963).

The purpose of the present study was to investigate whether contraceptive treatment in healthy women of child-bearing age has any effect on the urinary excretion of porphyrin precursors and coproporphyrin, and on the coproporphyrin isomer distribution.

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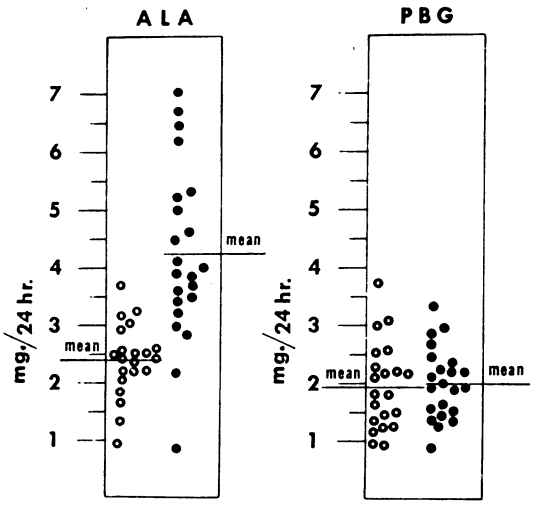
Material and Methods

The series comprised 43 healthy ambulatory women. Twenty-one of them served as controls. Twenty-two women who had taken oral contraceptives cyclically for at least three months formed the experimental group. The ages in the control group ranged from 17 to 47 years, the mean age being 31.3 years. The mean age in the experimental group was 31.7 years and the range from 23 to 48. The oral contraceptive preparations used were Volidan (4 mg. of megestrol acetate and 0.05 mg. of ethinyloestradiol), Anovlar (4 mg. of norethisterone acetate and 0.05 mg. of ethinyloestradiol), and Lyndiol (2.5 mg. of lynoestrenol and 0.075 mg. of mestranol). In seven instances two preparations had been used successively without interruption of the treatment. The names of the preparation and the number of cycles during which it had been used in each individual case up to the date of examination are given in the Table.

Urinary Excretion of δ-aminolaevulic Acid (ALA), Porphobilinogen (PBG), and Coproporphyrin (UCP) in Healthy Female Subjects on Oral Contraceptives. Where Two Preparations are Stated they were Used Successively without Interruption

Subject No.	Age	Preparation and Consumption Time in Menstrual Cycles	ALA	PBG	UCP			
			mg./24 hr.		Total	I	III	III % of Total
					μg./24 hr.			
22	26	Volidan 7½	3·00	2·08	73	18	55	75
23	32	Volidan 4 and Anovlar 2½	3·21	2·87	64	25	39	61
24	33	Anovlar 6 and Lyndiol 2½	2·14	1·39	70	14	56	80
25	43	Volidan 2 and Lyndiol 8	3·60	2·70	67	35	32	48
26	28	Volidan 1½ and Anovlar 3½	5·25	2·27	66	15	51	78
27	27	Volidan 6½	3·89	2·18	100	20	80	80
28	37	Volidan 14½	4·50	1·97	51	13	38	74
29	25	Lyndiol 13½	3·81	1·54	115	25	90	78
30	31	Anovlar 6½	4·10	2·02	59	15	44	75
31	29	Volidan 1 and Anovlar 3½	6·15	1·24	69	22	47	68
32	29	Volidan 10½	7·02	2·34	73	13	60	82
33	29	Volidan 5½	3·40	1·63	75	25	50	67
34	23	Lyndiol 3	4·58 (2·11)*	1·46 (0·95)	117 (82)	55 (24)	62 (58)	53 (71)
35	35	Volidan 15½	3·71	1·49	39	—	—	—
36	30	Volidan 6 and Lyndiol 1½	2·86	2·20	104	—	—	—
37	35	Volidan 6½	6·73	2·96	62	—	—	—
38	33	Volidan 5	5·33	2·49	54	12	42	78
39	38	Volidan 4½	3·50	0·90	50	—	—	—
40	40	Volidan 6½	5·02	1·88	81	—	—	—
41	48	Anovlar 3 and Volidan 5½	3·98	1·94	53	—	—	—
42	33	Anovlar 5	6·45	3·35	53	17	36	68
43	27	Volidan 6	0·86	1·87	80	—	—	—

* Values given in parentheses were obtained one month after discontinuation of the drug.



○ CONTROL SUBJECTS

● SUBJECTS ON ORAL CONTRACEPTIVES

Urinary excretion of δ-aminolaevulic acid (ALA) and porphobilinogen (PBG) in healthy females of child-bearing age.

The urine was collected during each 24-hour period, stored alkaline, and protected from light. The urine collections were made in each case towards the end of the cycle. ALA and PBG determinations were carried out according to the method of Mauzerall and Granick (1956). Coproporphyrin determinations were made as described by Koskelo (1956). Coproporphyrin isomers I and III were separated by thin-layer chromatography according to Jensen (1963). The separated isomers were eluted from the plates and measured fluorometrically. Details of the isomer analysis and the normal values obtained by it are given elsewhere (Koskelo and Toivonen, 1965).

Results

The results are shown in the Table and the Figure.

δ-Aminolaevulic Acid.—The mean 24-hour urinary excretion of ALA in 21 control subjects was 2.41 mg. The values varied in individual cases over a range of 0.94 to 3.70 mg./24 hr. The standard deviation was 0.64 mg./24 hr. The mean excretion of ALA in 22 experimental subjects was 4.23 mg./24 hr., the range from 0.86 to 7.02, and the standard deviation 1.53 mg./24 hr. A comparison of the mean excretion of ALA of subjects on oral contraceptives with the mean value of the control subjects gives a statistically highly significant difference ($P<0.001$). When values from 1.13 to 3.69 mg./24 hr.—obtained by multiplying the standard deviation on both sides of the mean by two—are regarded as the normal range, it can be stated that the urinary excretion of ALA was above normal in 14 cases, equivalent to about 64% of the treated cases. There was no correlation between the urinary ALA excretion and the duration of treatment. All of the three contraceptive preparations tested in this study seemed to have an equal effect on the ALA excretion.

Porphobilinogen.—The mean 24-hour urinary excretion of PBG in the control group was 1.95 mg. The values varied in individual cases over a range of 0.95 to 3.77 mg./24 hr. The standard deviation was 0.75 mg./24 hr. The corresponding values for PBG in the experimental group were: mean 1.99, range 0.90–3.35, and standard deviation 0.53 mg./24 hr. There is no statistically significant difference between the means in these two groups.

Coproporphyrin.—The urinary coproporphyrin excretion varied in the experimental group from 39 to 117 μg./24 hr. The mean was 72 and the standard deviation 21 μg./24 hr. A comparison of the mean coproporphyrin excretion in this group with the mean excretion of 18 healthy subjects (63 μg./24 hr., S.D. 21) studied by Koskelo and Toivonen (1965), or with the mean excretion of 33 healthy subjects (64 μg./24 hr., S.D. 30) studied by Koskelo (1956) by the same method, shows that there is no statistically significant difference between these means. The coproporphyrin isomer distribution was studied in 15 out of the 22 cases in the experimental group. The mean excretion of isomer I was 22 μg./24 hr. (S.D. 11) and that of isomer III 52 μg./24 hr. (S.D. 16). The mean excretion of isomer III was 71.0% (S.D. 10.2) of the total urinary coproporphyrin output. The corresponding means in the control group of 18 healthy subjects (see Koskelo and Toivonen, 1965) were: isomer I 14 μg./24 hr. (S.D. 4), isomer III 49 μg./24 hr. (S.D. 18), and isomer III content expressed as percentage of total 77.4 (S.D. 4.8). Although the total coproporphyrin output was not significantly affected by the treatment, a comparison of the means of the two isomers reveals, however, that the treated cases excrete on an average more coproporphyrin I than the controls. The difference is highly significant ($P<0.001$). The large preponderance of isomer III tends to overshadow the changes in coproporphyrin as a whole. The mean isomer III content (percentage of total) is almost significantly lower in the treated group ($0.05>P>0.025$), but there is no significant

difference between the means of isomer III excretion (μg./24 hr.).

Discussion

The bone-marrow and the liver are the principal sites of the haem synthesis, though nearly every living cell is able to synthesize this chromogen. Numerous experimental and clinical investigations have indicated that the haem synthesis is affected in the bone-marrow by certain heavy metals and in the liver by some chemical substances and drugs (Goldberg and Rimington, 1962 ; Schmid, 1963). Impaired liver function is frequently observed after oral contraceptives (Eisalo *et al.*, 1964, 1965) and it is evident from the present work that they often also affect the porphyrin metabolism.

The accurate mechanism which causes increased ALA excretion in healthy females taking oral contraceptives is not known and is a matter of speculation only. It may be easier to explain the increased proportion of coproporphyrin I in the urine. The urinary excretion of coproporphyrin I is distinctly increased in non-alcoholic cirrhosis, obstructive jaundice, and acute hepatitis. Intrahepatic cholestasis is the dominant factor causing partial transfer of type I coproporphyrin, normally excreted in the bile, to the blood and urine (Aziz *et al.*, 1964). The increased proportion of coproporphyrin I in urine with a normal total urinary coproporphyrin excretion seen in our treated cases may be regarded as a sign of a relatively mild liver functional impairment. The observations of Eisalo *et al.* support the above assumption.

Though the impairment in liver function is in most cases mild, it may in some cases be more severe. An example of this is Case 34 in our series. This patient developed cholestatic jaundice after taking an oral contraceptive for three months.

Summary

Urinary excretion of δ-aminolaevulic acid, porphobilinogen, and coproporphyrin was studied in 22 healthy women of child-bearing age on oral contraceptives. The mean excretion of δ-aminolaevulic acid was significantly higher than the mean excretion in a control group of 21 women. There was no significant difference in the excretion of porphobilinogen in the two groups. Total coproporphyrin was normal in every case, but the study of isomer distribution in 15 cases revealed a higher mean isomer I content than normally.

The possible mechanisms which cause these changes are discussed.

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Medical Memoranda

Acute Transverse Myelitis as a Complication of Glandular Fever

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Acute transverse myelitis has been recognized as a clinical entity for several decades. Nevertheless it remains a poorly understood syndrome, not only aetiologically but also in terms of its clinical behaviour. We record below a case of this syndrome where the cause was shown to be glandular fever.

Case Report

A 28-year-old housewife was admitted to hospital on 8 July 1964. For two weeks previously she had felt generally unwell, with a temperature and sore throat. Three days before admission she had begun to notice an alteration in sensation in her legs, and they had become so tender that she could not bear them to be touched. Over this period she had also suffered from frequency and urgency of micturition with alteration in urethral sensation. In the 48 hours immediately before admission she had been unable to pass any urine, and there had also been a rapidly progressive weakening of the legs, so that on admission she was unable to walk.

On examination she was febrile (oral temperature 102° F. (38.9° C.)). There was no pharyngitis, and no lymphadenopathy, and her spleen was not palpable. Her urinary bladder was distended, without pain, to above the umbilicus. Neurological examination of the cranial nerves and upper limbs was normal. In the legs tone was decreased, with marked symmetrical weakness of all muscle groups ; the hip flexors, hamstrings, and dorsiflexors of the feet being particularly affected. All her deep tendon reflexes were brisk—this was very noticeable in the legs—and the plantar responses were bilaterally extensor. Her abdominal reflexes were absent. There was a sensory level to pinprick, light touch, and temperature sense below D4, but position and vibration senses were still present in the feet.

During the 48 hours after admission she developed a total areflexic paralysis of her legs, with complete loss of all sensory modalities below a level at D3. For a few days only there was slight weakness of the small muscles of the hands, so that she had difficulty in handling a knife and fork. Her spleen, which had not been palpable on admission, now became enlarged to 3 cm. below the costal margin.

Investigations showed: haemoglobin 12.5 g./100 ml. (86%) ; W.B.C. 6,000/c.mm., of which 54% were neutrophils and 46% lymphocytes ; platelets 217,000/c.mm. ; E.S.R. 26 mm. in one hour (Westergren). Blood film showed a few atypical mononuclear cells, and the Paul-Bunnell screening test was positive. Serum absorbed with saline gave a Paul-Bunnell titre of 1:448 ; with guinea-pig kidney cells the titre was 1:224 ; and with ox red cells it was less than 1:7. These findings confirmed the diagnosis of glandular fever.

Radiographs of chest, skull, and spine were normal. An emergency myelogram, performed on the day of admission to exclude an extradural abscess, revealed no abnormality. The cerebrospinal fluid, at a pressure of 150 mm. of fluid, contained 100 mg./100 ml. of protein, with a moderate excess of globulin, and 2 lymphocytes/