Occasional Survey

Kidney Disease and Pregnancy

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Summary

The course of 41 pregnancies was studied in 25 patients with renal disease. Histological classification of the disease in each patient was made by renal biopsy. The analysis suggests that the course of pregnancy in women with coexistent renal disease correlates with the underlying renal lesion and probably with the glomerular filtration rate and blood pressure. In patients with heavy proteinuria there is increased oedema formation, making the nephrotic syndrome a frequent complication.

Introduction

The effect of pregnancy on the course of coexistent renal disease as well as the influence of renal disease on the development of conceptus and the appearance of complications of pregnancy are not clear. Though earlier reports suggested a poor outlook for pregnant women with renal disease,[1-3] recent studies have indicated that in the absence of renal insufficiency or severe hypertension the incidence of important complications is minimal and fetal survival is good.[4-7] Most studies of pregnant women with coexistent renal disease, however, have not given sufficient information to provide a useful guide in counselling patients with pre-existing renal disease who want to become pregnant or in clinical management after the onset of gestation.

Since the course of renal disease in non-pregnant patients is known to be closely related to the underlying renal lesion,[8] it seemed likely that this factor, as well as functional correlates, might also play an important part during pregnancy. This report analyses our experience during 41 pregnancies in 25 women in whom pre-existing renal disease was established or in whom renal disease was initially diagnosed during pregnancy. Histological classification was made in all patients from material obtained by renal biopsy.

Patients and Methods

Patients included in this report were referred to the renal section of the Yale-New Haven Hospital for diagnostic evaluation. Percutaneous renal biopsy was performed before or after pregnancy, and tissue examined by light microscopy and electron-microscopy.[5] At the time of evaluation, in addition to careful history-taking and physical examination, studies included measurement of blood urea nitrogen, serum creatinine, serum protein with fractionation, quantitative urine protein excretion, β_1C globulin, and antinuclear factor and L.E. cell preparation and intravenous pyelography. Further information about previous laboratory studies and earlier pregnancies was obtained from hospital records and referring doctors.

The clinical diagnosis of systemic lupus erythematosus (S.L.E.) was based on the presence of a L.E. cells and antinuclear factor test result as well as on the characteristic clinical features of this disease. The renal histological classification was made by Dr. Michael Kashgarian, of the Department of pathology. Proliferative glomerulonephritis was characterized by an increased number of intraglomerular cells and mesangial matrix. In chronic glomerulonephritis the predominant change was glomerular hyalinization and interstitial fibrosis, often associated with proliferation of intraglomerular cells. The lesion of membranoproliferative glomerulonephritis was recognized by the characteristic lobular pattern and split basement membrane on silver methionine stains. Plasma levels of β_1C globulin were also persistently depressed in each of the two patients with this type of disease. In membranous nephropathy the basement membrane was irregular, the epimembranous spike and dome pattern was found on silver stains, and epimembranous and intramembranous electron-dense deposits were present on ultrastructural examination. The classification used to designate the lesion in patients with lupus glomerulonephritis has recently been reported.[9] In this study one patient had mild lupus glomerulonephritis, class I, while the remaining eight cases showed a diffuse lupus glomerulonephritis, class III, on renal biopsy. The single patient with diabetic glomerulosclerosis had a moderately severe nodular lesion.

The nephrotic syndrome was defined as heavy proteinuria, exceeding 4·0 g/day, and a serum albumin level less than 3·0 g/100 ml. This condition was usually associated with oedema and raised serum lipids.

Results

The pertinent clinical features during pregnancy and at the end of follow up are shown in the table.

PROLIFERATIVE GLOMERULONEPHRITIS

Proliferative glomerulonephritis was found in four cases. In three patients (cases 1, 2, 3) the changes were characterized by a mild diffuse pattern of hypercellularity, while in one patient (case 4) a severe crescentic change was found. In each case the apparent onset of renal disease occurred during the first pregnancy. Persistent proteinuria was noted during pregnancy in the patient in case 3 who subsequently showed signs of the nephrotic syndrome and severe hypertension two weeks post partum. Over the next six months her blood pressure and protein excretion returned to normal. The nephrotic syndrome began in the fifth month of gestation in case 1 and responded, with a complete remission, to treatment with glucocorticoids. A recurrence one to two months post partum spontaneously remitted. There was

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no evidence of renal disease during six subsequent pregnancies in this patient; and eleven years later the urine was free of protein and renal function was normal. The patient in case 2 developed intermittent gross haematuria during pregnancy, in the absence of hypertension or reduction infiltration rate. At the time renal biopsy was performed, 18 months post partum, proteinuria had persisted. The nephrotic syndrome and renal insufficiency occurred early in gestation in case 4, resulting in a spontaneous abortion in the fourth month. Within several weeks after the termination of pregnancy chronic haemodialysis was instituted, and a successful cadaveric transplantation was performed six months later.

CHRONIC GLOMERULONEPHRITIS

In the five patients with chronic glomerulonephritis renal disease antedated pregnancy in three and was recognized during pregnancy in two others. The nephrotic syndrome was present in each patient in at least one pregnancy and, in general, complications were more frequent in this group than in patients with other types of lesions. One patient (case 5) developed the nephrotic syndrome two years before the first pregnancy, and it remitted spontaneously. Both subsequent pregnancies (shown in the table) were relatively uncomplicated except for transient recurrence of nephrosis and moderate hypertension during the

Summary of Clinical Data on Pregnant Women with Renal Disease

Case No.	Onset of Renal Disease (Month/yr)	Onset of Pregnancy (Month/yr)	During Pregnancy: Max. B.P. (mm Hg)	B.U.N./Cr. (mg/100 ml)	S. Alb. (g/100 ml) Ur. Prot. (g/day)	Oedema	Product Conception: Type of* Delivery/Birth Weight (g)	Apgar	Comments	Date of Renal Biopsy	End of Follow up: Date	B.P. (mm Hg)	B.U.N./Cr. (mg/100 ml)	Ur. Prot.	Oedema
Mild Proliferative Glomerulonephritis															
1	1/60	9/59	120/80	8/0·9	1·1/14·7	Moderate	F.T./2,350	9	Nephrotic	9/60					
		1/62	120/80	8/0·8	3·2/0·3	0	F.T./2,370	good	Uncomplicated						
		1/63	120/80	7/1·0	2·8/0·1	0	F.T./2,450	8–10	Uncomplicated						
		2/64	120/70	—	–/0	0	F.T./2,125	9–10	Uncomplicated						
		7/65	120/88	—	–/0	0	S.A.(7 mnth)		Uncomplicated						
		11/67	120/80	—	–/0	0	F.T./2,735	9–10	Uncomplicated						
		8/69	128/90	—	–/0	0	F.T./2,115	9	Uncomplicated		1/71	130/90	14/–	0	0
2	3/70	12/69	120/80	10/–	3·3/2+	0	F.T./3,620	9	Gross Hematuria	2/72	3/72	120/70	16/1·0	2·6	0
3	1/72	10/71	130/90	7/0·8	–/1·9	0	F.T./3,210	9	Nephrosis and hypertension postpartum	10/72	1/73	110/80	14/1·2	0·2	0
Severe Proliferative Glomerulonephritis															
4	11/69	10/69	140/96	43/2·3	2/0·4+	Marked	S.A. (4 mnth)		Nephrotic uraemia	1/70	5/73	Transplantation in 8/70			
Chronic Proliferative Glomerulonephritis															
5	6/68	5/70	130/95	13/1·7	0·7/13·2	Moderate	F.T./2,330	9	Hypertension postpartum						
		2/71	125/80	—	–/1+	0	F.T./2,200	6	Uncomplicated	3/72	3/72	140/85	16/–	2·5	0
6	2/69	12/68	140/110	28/1·9	0·7/13	Moderate	28wk/885	3–5	Nephrotic hypertension	9/69					
		12/69	110/80	15/1·3	2·0/6·7	0	T.A. (2 mnth)		Uncomplicated		3/72	130/90	22/–	2·5	0
7	10/70	7/70	130/90	43/2·0	1·4/13	Severe	F.T./2,065	8	Nephrotic hypertension postpartum	7/71	1/72	110/80	33/–	1·5	0
8	11/66	5/67	120/80	19/1·3	0·8/9·6	Severe	T.A. (5 mnth)		Nephrotic	11/66	5/73	Haemodialysis since 5/70			
9	6/61	2/63	150/80	—	–/4+	Mild	F.T./–		Nephrotic						
		5/66	140/80	28/–	1·9/4+	Severe	F.T./2,400		Nephrotic	2/67	8/68	120/80	22/2·2	6·8	0
Membranoproliferative Glomerulonephritis															
10	3/69	1/69	120/80	11/0·9	2·0/4·5	Severe	T.A. (2 mnth)		Nephrotic						
		9/70	120/70	20/1·1	1·9/3·0	Moderate	F.T./2,850	9	Nephrotic	6/71	6/71	120/80	21/1·0	4·0	0
		7/66	—	9/–	–/1+	(	F.T./2,875	9	Uncomplicated	11/69					
11	12/69	1/70	—	—	–/0·5	0	T.A. (2 mnth)		Uncomplicated	5/71					
		9/71	150/94	13/0·8	–/2+	0	F.T./2,830	9	Uncomplicated		2/73	110/78	13/0·8	1+	0
Membranous Nephropathy															
12	5/65	3/65	120/90	9/0·7	2·5/10	Mild	F.T./–	good	Nephrotic						
		3/66	120/80	6/1·1	–/3+	Moderate	F.T./–		Nephrotic	6/68					
		4/68	110/70	11/–	–/2+	0	T.A. (2 mnth)				11/68	120/80	11/–	1+	0
13	10/65	1/69	130/90	20/–	3·5/0	0	F.T./2,925	9	Uncomplicated	5/66	2/73	170/100	11/1·1	0	0
14	9/55	6/55	148/100	—	–/4+	Mild	F.T./–	good	Nephrotic	6/59					
		4/62	150/90	7/1·0	3·2/0·2	0	F.T./2,475	9	Uncomplicated		11/68	140/100	—	2+	0
15	12/64	10/64	130/80	9/–	–/2+	Moderate	F.T./4,950	good	Nephrotic						
		4/65	130/90	10/0·8	1·9/4·1	Moderate	F.T./4,050	good	Nephrotic	4/72	4/73	110/70	10/1·0	7·8	0
Diabetic Glomerulosclerosis															
16	5/67	7/67	140/90	22/0·4	2·2/6·6	Mild	T.A. (3 mnth)		Nephrotic	4/68	11/72	120/85	25/–	4·7	0
Mild Lupus Glomerulonephritis															
17	11/65	3/69	120/100	17/1·2	–/1·7	Mild	F.T./1,910	8	Postpartum vasculitis		2/73	140/100	–/1·0	1+	0
Diffuse Lupus Glomerulonephritis															
18	3/69	8/68	120/80	—	–/0·7	Mild	F.T./3,230	7	Postpartum depression	12/69	11/72	135/95	16/0·7	0·4	0
19	3/66	3/70	150/120	44/1·5	–/2·2	Mild	F.T./1,920	9	Hypertension and postpartum heart failure	12/70 4/69	4/71	140/100	24/1·3	1+	0
20	4/69	6/70	120/80	13/0·8	–/0·1	0	F.T./3,205	8	Uncomplicated	5/72	10/72	115/70	10/1·0	0·1	0
21	6/70	4/70	150/84	—	–/4+	Mild	F.T./3,400	7–10	Onset S.L.E. 2nd Month of pregnancy	5/71	5/71	130/78	22/0·9	0·7	0
22	1/68	12/68	120/80	10/1·1	–/0	0	T.A. (2 mnth)		Uncomplicated	1/68	5/73	Uraemia-haemodialysis—12/70			
23	6/64	5/69	170/130	12/1·2	0/0·7	Mild	F.T./3,110	2–5	Hypertension and postpartum arthralgia	5/70	10/72	150/100	15/1·2	0	0
24	4/64	7/65	135/100	49/1·1	–/2+	Mild	S.A. (6 mnth)		Uncomplicated	2/65	Exacerbation 1 yr postpartum Death renal failure—3/67				
25	3/67	9/66	140/100	—	–/4+	Severe	F.T./–		Onset S.L.E. 7th Month of pregnancy Nephrotic	8/67	Death renal failure—9/67				

*F.T. = Full term. S.A. = Spontaneous abortion or stillbirth. T.A. = Therapeutic abortion.
B.U.N./Cr. = Blood urea nitrogen/serum creatinine.
S.Alb./Ur. Proc. = Serum albumin/urine protein.

first pregnancy. Her blood pressure suddenly increased to levels of 180/120 mm Hg several weeks after the delivery of her first child, needing antihypertensive therapy, but remained within normal range during and after the second pregnancy. A similar acceleration of hypertension post partum occurred in case 7, but it persisted, antihypertensive therapy being needed to reduce blood pressure to normal levels. Apparently, therefore, pregnancy had a mitigating effect on blood pressure in these two patients. In contrast, the severe hypertension which occurred during pregnancy in case 6, associated with the nephrotic syndrome, decreased post partum to a slightly raised level. Of special interest in four patients (cases 5, 6, 7, 9) was a spontaneous decrease in oedema and rise in serum albumin levels post partum.

A therapeutic abortion was performed in case 8 because of severe oedema which was inadequately controlled by diuretic agents and in case 6 because of a complicated earlier pregnancy. There was no apparent change in filtration rate in relation to pregnancy in any patient.

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

The diagnosis of membranoproliferative glomerulonephritis was made in two women in association with five pregnancies. One patient (case 10) developed the nephrotic syndrome in the first trimester of her initial pregnancy. A clinical diagnosis of probable acute postinfectious glomerulonephritis was made because of the finding of many free red blood cells and red blood cell casts in the urinary sediment though serological and cultural studies for a streptococcal infection were negative. Pregnancy was terminated in accordance with the wishes of the patient and her family. Oedema completely subsided post-partum, and urine protein levels were recorded as 2+. Recurrence of the nephrotic syndrome in the first trimester of this second pregnancy was easily controlled with dietary salt restriction and intermittent use of diuretics. Spontaneous reduction in oedema occurred post-partum.

Renal evaluation was performed in case 11 because asymptomatic proteinuria was found during and after her first pregnancy. The renal biopsy performed in November 1969 showed an active proliferative glomerulonephritis with focal areas of necrosis and mesangial electron-dense material. While levels of β_1C globulin were persistently depressed, serological studies for S.L.E. were negative. Because of the uncertain rate of progression of this lesion termination of her second pregnancy was advised. The second renal biopsy, 18 months later, showed characteristic changes of chronic membranoproliferative glomerulonephritis. Since renal function remained stable throughout the period of observation the patient elected to continue with her plans for another pregnancy, which was uncomplicated except for mild hypertension.

MEMBRANOUS NEPHROPATHY

The four patients with membranous nephropathy were observed through eight pregnancies and, in general, they experienced relatively uncomplicated courses. In three patients (cases 12, 14, and 15) the nephrotic syndrome occurred during the first pregnancy. Oedema was controlled during the initial and subsequent pregnancies and apparently subsided spontaneously during the post-partum periods. One patient (case 13) maintained complete remission throughout pregnancy two years after a reduction in proteinuria that was associated with prednisone and azathioprine treatment.

The spontaneous variations in urinary protein excretion and a persistence of normal renal function for long periods in these patients is consistent with recent reports [9-10] that membranous nephropathy is a slowly progressive and indolent disease.

DIABETIC GLOMERULOSCLEROSIS

The single patient (case 16) with diabetic glomerulosclerosis developed nephrotic syndrome two months before conception. Because of the severity of the lesion and mild hypertension found early in pregnancy termination was advised. In contrast to the expected rapid decline in renal function and persistence of heavy proteinuria, subsequent observations showed a spontaneous fall in proteinuria and maintenance of function for the next four years. This patient adopted a child.

LUPUS NEPHROPATHY

There were nine patients with lupus glomerulonephritis. In eight cases the histological classification was class III, and in one patient it was class I. Renal disease antedated the onset of pregnancy from a few months to several years in all except three patients, in whom systemic manifestations and renal disease first occurred during pregnancy. As shown in the table, the manifestations of the primary disease during and immediately after pregnancy varied widely.

In the six women with pre-existing lupus nephritis three (cases 20, 22, and 24) experienced little change in their otherwise stable course. A therapeutic abortion was performed in case 22 because of the possible teratogenic effects of azathioprine, which had been given during the first two months of gestation. In case 20 azathioprine had also been given during the first trimester. When the patient refused termination of pregnancy azathioprine was discontinued while prednisone was continued in a dose of 7·5 mg/day. No evidence of recurrence of systemic or renal manifestation was observed during or after pregnancy. Azathioprine was reinstituted immediately after delivery. A stillborn baby was delivered to the third patient (case 24) after six months of gestation though the primary illness had remained relatively stable. The exacerbation of lupus which caused death from renal failure 12 months later seemed to be unrelated to the pregnancy.

In the remaining patients with antecedent lupus nephritis varied complications occurred within a few months post-partum, including cerebral vasculitis (case 17), severe hypertension, and heart failure (case 19), and moderate hypertension and arthralgia (case 23). The clinical course had been mild and stable before pregnancy, and in each case the post-partum exacerbation resolved spontaneously or responded to a temporary increase in specific therapy. It could not be determined whether the depression experienced by the patient in Case 19 was related to her primary disease.

Of the three cases in whom S.L.E. apparently first occurred during pregnancy one (case 25) had a rapidly progressive course and died a few months post-partum. The remaining two had persistent proteinuria, stable renal function, and suppression of systemic manifestation on low doses of prednisone.

CONCEPTUS

Of the 41 pregnancies there were 31 live births, eight abortions (one spontaneous and seven therapeutic), and two still births. There was information on the birth weight of 26 infants (mean ($\pm$ S.D. 2,716 g $\pm$ 793). Only three infants were under 2,000 g, and the one severely premature infant (885 g) was delivered at 28 weeks by section because of severe hypertension. There was no early postnatal mortality in any of the live births.

Of the seven therapeutic abortions, only one (case 8) was performed because of increased symptoms due to renal disease. This patient developed increasing oedema, unresponsiveness to diuretic agents, and a definite fall in serum albumin levels to less than 1·0 g/100 ml in the first trimester. In the remaining cases abortion had been advised because of known pre-existing

renal disease and the anticipation of complications during pregnancy. Social reasons played a major additional part in two of these. One stillbirth (case 1) occurred at seven months unassociated with any evidence of renal disease, and the second occurred in case 24 with stable lupus glomerulonephritis.

NEPHROTIC SYNDROME

The nephrotic syndrome occurred in 13 women—about half of the group. In cases 4 and 25 heavy proteinuria was associated with a severe proliferative glomerulonephritis and rapidly declining function. In these patients the features of nephrotic syndrome were overshadowed by symptoms of uraemia. Progressive oedema unresponsive to conservative treatment played a major part in the decision to terminate pregnancy in case 8.

In the remaining 10 women with nephrotic syndrome during pregnancy oedema was adequately controlled by the dietary restriction of sodium and the intermittent use of diuretics. As noted previously,[11 12] the accumulation of oedema fluid seemed to subside spontaneously during the post-partum period. In five cases 6, 7, 8, 9, and 10 that we closely followed during pregnancy the reduction in oedema post-partum was associated with a rise in serum albumin levels, usually in the absence of a change in the amount of proteinuria.

Four patients (cases 1, 5, 13, and 22) became pregnant after a complete or partial remission of a preceding episode of the nephrotic syndrome had occurred. None of these cases experienced a recurrence in association with pregnancy.

Discussion

It seems clear from these data and from previous reports, recently reviewed,[6 13] that a satisfactory course of pregnancy can be expected in most women with coexistent primary renal disease in the absence of renal insufficiency or severe hypertension before the onset of gestation. There is no evidence that pregnancy causes a deterioration of renal function or otherwise affects the rate of progression of the renal lesion beyond what might be expected in the non-pregnant state. The inexorable rapid decline in renal function in case 4 was typical of the clinical course of crescentic glomerulonephritis.[14] The type of renal disease found in any group of pregnant women studied will, therefore, influence the outcome of the group. Moreover, an apparent fall in glomerular filtration rate during pregnancy in patients with the nephrotic syndrome[11] may reflect pre-renal factors since hypoalbuminaemia is often accentuated.

In our 15 patients with primary renal disease the major complications included an increase in oedema and raised blood pressure. Exaggeration of oedema during pregnancy and the tendency for spontaneous improvement in the post-partum period has been noted previously[11 12] and may relate to more definite changes in serum albumin levels due to increased protein requirements by fetal and maternal tissues.[11] In contrast to previous studies, however, oedema was usually easily controlled in this group of patients without the necessity for prolonged periods of bed rest—possibly owing to the current availability of potent diuretic agents, such as frusemide, which are effective in pregnancy.[15] Indeed termination was performed in only one of our patients because of refractory oedema. Adequate control of oedema might have also contributed to the absence of post-partum sepsis and thrombotic complications that was observed in seven cases with membranous nephropathy[12 16] Since women with a previous episode of the nephrotic syndrome have often been considered a special risk group because of the possibility of recurrence it is noteworthy that four patients with persistent renal disease in partial or complete remission did not relapse.

Appreciable hypertension was not often found and was usually responsive to antihypertensive agents, such as the thiazides and hydrallazine. Hypertension was a major complication in one patient with chronic glomerulonephritis (case 6) and accounted for the single caesarean section and premature infant in this group. In two other cases with lupus glomerulonephritis severe hypertension occurred transiently post-partum. It was of interest that pregnancy had a paradoxical influence on blood pressure resulting in an apparent lowering effect in two patients.

Reports of an increased incidence of toxaemia in women with the nephrotic syndrome,[5] especially in cases with pre-existing renal insufficiency,[3] are difficult to interpret. The clinical criteria used in establishing the syndrome of toxaemia are the same features exhibited by the renal disease. Until specific criteria are available for the diagnosis of toxaemia this classification should probably not be used in patients with coexistent renal disease.

Most of these pregnancies—75%—resulted in healthy live births. The fetal survival in this group compares favorably with that in other reports with the nephrotic syndrome[11 12] and without the nephrotic syndrome. As suggested previously,[3] probably most of the pregnancies which were terminated by therapeutic abortion would also have resulted in live births, with a similar incidence of complications, if allowed to continue. In a study of 26 pregnancies fetal birth weight was found to be related to the level of serum albumin in the mother.[11] Though a similar analysis in this study was precluded by the lack of adequate data the average birth weight of six full-term infants born to six nephrotic women was 2,683 g, a value somewhat less than the expected mean of 3,200 g.[18] Nevertheless, the average Apgar score of 8·7, excluding the one premature infant, was similar to values found in normal full-term infants in the United States.

Of the patients in this series 40% had S.L.E. with lupus glomerulonephritis. These patients deserve special attention since the effect of pregnancy on lupus nephropathy and non-renal manifestations of S.L.E. as well as on the systemic features has not been clear. Since lupus glomerulonephritis, usually associated with a poor outlook, was found by biopsy in eight or nine patients it was somewhat surprising that renal function and the level of proteinuria remained stable during and for several months after pregnancy. Case 25 was the exception in the group and pursued a hectic course after S.L.E. occurred in the last trimester of pregnancy. The experience with the group was, therefore, similar to that found in patients with non-lupus glomerulopathy.

The effect of pregnancy on the overall activity of S.L.E. is much more difficult to analyse. Previous studies have suggested that patients with pre-existing S.L.E. have more exacerbations during pregnancy and post-partum.[19] Though three cases in this category developed appreciable non-renal complications after pregnancy, the few patients and the variability of the course for this disease preclude a clear resolution of the question in this study, as well as in earlier reports.[20] Until a carefully performed prospective evaluation is made available consideration of possible special risks from the systemic features of S.L.E. must be included in counselling women on the possible hazards of pregnancy.

This analysis suggests that the course of pregnancy in women with coexistent renal disease correlates with the underlying renal lesion and probably with the glomerular filtration rate and blood pressure. In the absence of renal insufficiency or severe hypertension the likelihood of significant complications is small and the chance of obtaining a healthy infant is excellent. In patients with heavy proteinuria there is a pervading tendency to increased oedema formation, so that women with this condition should be prepared to accept this controllable complication when contemplating pregnancy. There is less information about the prognosis of pregnancy in patients with renal insufficiency though, as suggested previously, the outlook in this group is probably more guarded.

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Imported Diseases in General Practice

Check-ups After Travel

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Persons having entered this country are often referred at their own or their doctors' request for a "check-up"; some who work overseas are regularly seen during their home leave at their own request or that of the firm or organization which employs them. Such persons may be divided into (*a*) those who have made a comparatively short visit overseas as a traveller or under the auspices of a voluntary organization; with the great increase in travel some may spend one or two years sometimes working, sometimes moving about the world; (*b*) those who work overseas in the employ of British firms, foreign governments, the British Government, or missionary societies; such persons spend longer periods abroad. Missionaries especially may live in rural areas, whereas others may spend most of their time in or around large towns; (*c*) those entering Britain for the first time as immigrants or visitors; there has been a great increase in the number of those travelling overland from Australia and New Zealand, through Asia to this country.

Those seen may have been in any part of the world but at present those from India, Pakistan, and the Far East constitute the largest group followed by those from Africa and then the Middle East, South America, and New Guinea. Though visitors to parts of Europe not infrequently require medical attention on their return to this country they seldom request a check.

The circumstances under which individuals have lived before entering this country vary greatly; at one extreme are those who have spent a short time in a top-grade hotel in a large tropical city and those who have lived in their own house with good facilities—water supply, sewage disposal, fly screening, and perhaps air-conditioning. At the other extreme are those who have "lived rough," sometimes by intention and sometimes because their money has run out or because they have been ill. Some have lived in religious institutions or with nomads; some have worked under poor conditions in refugee camps; and some in street dispensaries in the slums of a large town. Immigrants often visit their home country after years in Britain and perhaps spend several weeks in an African village or a small Indian town. Some make their journeys by air, some by train and bus; some hitchhike; many travel in parties in Land Rovers; and at least one person I saw made a long journey alone and on a bicycle.

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Symptoms

There are those who remain perfectly well but they constitute a small minority; one young man wandered around Africa for five years sleeping outside, drinking water and eating food from any source; he took no malaria suppressives, he had no ill health whatsoever, and on investigation in London when he returned no parasite was found. Undoubtedly, diarrhoea is the commonest symptom of those travelling or living overseas. In many, though frequent, it is not incapacitating and is often considered a part of the visit. In some, however—and especially in those visiting Asian countries—it is severe, persistent, and debilitating; true dysentery in that blood is passed afflicts some, while in many there is loss of appetite and profound loss of weight.

Febrile episodes are less common but may be troublesome to children of families living overseas; jaundice again especially occurs in overland travellers in Asia and some have long and severe illnesses. A history of skin troubles is sometimes obtained. This often sounds as though prickly heat or a fungus infection has been responsible; skin irritation in those who have lived in West Africa suggest onchocerciasis, and haematuria a schistosome infection. Not infrequently patients have seen "worms" in their own or their children's stools.

Few patients have had any investigations while they have been abroad—or at best these have been inadequate: distances are great; travellers are often impecunious; and facilities are scanty. Some have had no treatment but "lie-up" for a few days; others have treated themselves with medicines they have taken with them or have bought locally—while some have sought medical attention, which has often resulted in multiple therapy with tablets, capsules, and injections partly owing to lack of diagnostic facilities. Very often the doctor here does not know what has been the matter when the patients present for a check in this country. Pyrexia is so often diagnosed as malaria, giving