1 McQueen FM, Stewart N, Crabbe J, et al. Magnetic resonance imaging of the wrist in early rheumatoid arthritis reveals a high prevalence of erosions at four months after symptom onset. *Ann Rheum Dis* 1998; **57:** 350–56.

2 Smolen JS, Aletaha D, Machold KP. Therapeutic strategies in early rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 2005; **19:** 163–77.

3 van Aken J, Lard LR, le Cessie S, Hazes JM, Breedveld FC, Huizinga TW. Radiological outcome after four years of early versus delayed treatment strategy in patients with recent onset rheumatoid arthritis. *Ann Rheum Dis* 2004; **63:** 274–79.

4 Grigor C, Capell H, Stirling A, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *Lancet* 2004; **364:** 263–69.

5 Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. *Arthritis Rheum* 2005; **52:** 3381–90.

6 Symmons D, Tricker K, Roberts C, Davies L, Dawes P, Scott DL. The British Rheumatoid Outcome Study Group (BROSG) randomised controlled trial to compare the effectiveness and cost-effectiveness of aggressive versus symptomatic therapy in established rheumatoid arthritis. *Health Technol Assess* 2005; **9:** iii–78.

7 Klareskog L, van der Heijde D, de Jager JP, et al for the TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) study investigators. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet* 2004; **363:** 675–81.

8 Wolfe F, Sharp JT. Radiographic outcome of recent-onset rheumatoid arthritis: a 19-year study of radiographic progression. *Arthritis Rheum* 1998; **41:** 1571–82.

9 Hulsmans HMJ, Jacobs JWG, van der Heijde DMFM, van Albada-Kuipers GA, Schenk Y, Bijlsma JWJ. The course of radiologic damage during the first six years of rheumatoid arthritis. *Arthritis Rheum* 2000; **43:** 1927–40.

10 Clarke AE, St-Pierre Y, Joseph L, Penrod JT, Sibley MH, Genant HK. Radiographic damage in rheumatoid arthritis correlates with functional disability but not the direct medical cost. *J Rheumatol* 2001; **28:** 2416–24.

11 Welsing PMJ, Landewé RBM, van Riel PLCM, et al. The relationship between disease activity and radiologic progression in patients with rheumatoid arthritis: a longitudinal analysis. *Arthritis Rheum* 2004; **50:** 2082–93.

Somatisation: a joint responsibility of doctor and patient

Patients with medically unexplained symptoms are common in general practice,[1] and frequently seen by various specialists.[2] These patients are often portrayed as "difficult" or "heartsink": a burden to the doctor as well as to the health-care system,[3] because they show resistance to psychological explanations of their suffering and are always in quest of biomedical causes, which easily results in excessive use of health-care services and even risk of iatrogenic harm.[3] Over the years, many empirical studies have been published about this issue, but nearly all focus on patients' characteristics and roles in the process. The possibility that doctors themselves play a part in the somatising process has been largely ignored.[4]

This possibility was explicitly examined by a research group from Liverpool University.[5–7] Adele Ring and colleagues[5] recently challenged the widespread belief of both researchers and doctors that inappropriate symptomatic treatment has to be attributed to patients' belief that symptoms are caused by physical disease, their consequent insistence on biomedical intervention, and their denial of psychosocial needs. Instead, they claim that the doctor is often responsible for the disproportionate levels of somatic interventions in this group of patients. By detailed analysis of 420 audiotaped consultations with patients with medically unexplained symptoms in general practice, the authors were able to show that physical interventions were proposed more often by doctors than by patients. Moreover, almost all patients provided cues to their psychological needs, whereas most doctors suggested that one or more physical diseases might be present. The authors conclude that the explanation for the high level of physical intervention in these patients lies in doctors' responses rather than patients' demands, and they propose that explanations for somatisation should be sought in doctor-patient interaction rather than in patients' psychopathology.[5]

Weighing the evidence of this study, two critical remarks have to be made. First, the doctors in this study indeed proposed a lot of biomedical interventions, but two-thirds also proposed non-medical explanations for patients' symptoms. Second, nearly 70% of the patients proposed some biomedical intervention, which is definitely higher than others have found in studies with a similar design,[8] so the possibility remains that with medically unexplained symptoms both doctor and patient are more active in advocating biomedical interventions. So, the evidence for the doctor's role in the somatising process could be strengthened by a replication of this study in a controlled design.

Nevertheless, the studies of the Liverpool group deserve further attention. They appeal to an approach that used to be present in psychiatry,[9] but seems to be lost in the current era of evidence-based medicine, which is primarily focused on patients' characteristics

and diagnostic criteria, while little interest is shown in the contribution of the doctor or of the doctor-patient relationship to the results of biomedical interventions.

Some circumstantial evidence supporting the findings is available. Several studies show that most doctors adapt their biomedical interventions at least partly to presumed patient preferences, while, at the same time, overestimating their patients' wish for biomedical interventions, including prescriptions and referrals,[10] resulting in unnecessary and even unwanted interventions.[11] So doctors' behaviour indeed might foster patients' somatic fixations.[4] But before we shift the blame and shame entirely from patient to doctor, it is relevant to analyse the contribution of both parties to the process of somatisation. The truth is that both patients and doctors have a preoccupation with finding biomedical causes for the presented health problems: patients because of their existential fear of serious diseases, doctors because of their professional pride and their fear for missing a medical diagnosis with all its potential judicial consequences. Hippocrates' oath, "first of all: do no harm", seems to be replaced by a new mantra: "first of all: don't miss a medical diagnosis" and, alas, there is a certain tension between these two guiding principles.[12] Another truth is that both patients and doctors are at a loss when no biomedical cause is discovered by diagnostic tests: patients because they feel humiliated and seen as malingerers; doctors because they do not feel equipped to deal effectively with medically unexplained symptoms.[13] A negative test result is bad news for patient as well as doctor. No wonder that many doctors and patients together land in a spiral of unnecessary biomedical interventions and growing frustration on both sides.[4,12]

Choosing the opposite strategy (attribution to psychological causes) is no alternative option, as most patients feel inadequately cared for when doctors "psychologise" their bodily suffering. The only option with medically unexplained symptoms is a comprehensive biopsychosocial approach right from the start, in which a biomedical track and a psychosocial track are jointly explored, thus giving the patients confidence that all biomedical needs are rightly addressed, while at the same time the floor is open for discussing the psychosocial issues that most patients are willing to discuss at the beginning of a new illness episode, but not after all medical examinations have failed to produce positive results. For when that moment has arrived, a psychological explanation is experienced as a second-rate explanation, by which many patients feel offended and humiliated.[14] How would you feel yourself?

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1 Rosendal M, Olesen F, Fink P. Management of medically unexplained symptoms et al. *BMJ* 2005; **330:** 4–5.
2 Wessely, S Nimnuan C, Sharpe M. Functional somatic syndromes: one or many? *Lancet* 1999, **354:** 936–39.
3 Rosendal M, Fink P, Bro F, Olesen F. Somatization, heartsink patients, or functional somatic symptoms? Towards a clinical useful classification in primary health care. *Scand J Prim Health Care* 2005; **23:** 3–10.
4 Biderman A, Yeheskel A, Herman J. Somatic fixation: the harm of healing. *Soc Sci Med* 2003; **56:** 1135–38.
5 Ring A, Dowrick CF, Humphries GM, Davies J, Salmon P. The somatising effect of clinical consultation: What patients and doctors say and do not say when patients present medically unexplained physical symptoms. *Soc Sci Med* 2005; **61:** 1505–15.
6 Ring A, Dowrick C, Humphris G, Salmon P. Do patients with unexplained physical symptoms pressurise general practitioners for somatic treatment? A qualitative study. *BMJ* 2004; **328:** 1057.
7 Salmon P, Dowrick CF, Ring A, Humphris GM. Voiced but unheard agendas: qualitative analysis of the psychosocial cues that patients with unexplained symptoms present to general practitioners. *Br J Gen Pract* 2004; **54:** 171–76.

8 Kravitz RL, Bell RA, Azari R, Kelly-Reif S, Krupat E, Thom DH. Direct observation of requests for clinical services in office practice: what do patients want and do they get it? *Arch Intern Med* 2003; **163:** 1673–81.

9 Balint M. The doctor, his patient and the illness. London: Pitman, 1957.

10 Little P, Dorward M, Warner G, Stephens K, Senior J, Moore M. Importance of patient pressure and perceived pressure and perceived medical need for investigations, referral and prescribing in primary care: nested observational study. *BMJ* 2004; **328:** 444.

11 Cockburn J, Pit S. Prescribing behaviour in clinical practice: patients' expectations and doctors' perceptions of patients' expectations—a questionnaire study. *BMJ* 1997; **315:** 520–23.

12 Grol R, ed. To heal or to harm. Prevention of somatic fixation. London: Royal College of General Practitioners, 1983.

13 Hartz AJ, Noyes R, Bentkler SE, Damiano PC, Wiollard JC, Momany ET. Unexplained symptoms in primary care: perspectives of doctors and patients. *Gen Hosp Psych* 2000, **22:** 144–52.

14 Malterud K. Humiliation, instead of care? *Lancet* 2005; **366:** 785–86.

Nuclear receptors, bile-acid detoxification, and cholestasis

Cholestasis (impaired secretion of bile) is characterised by increased serum and liver bile acids and other toxins. Treatment is difficult, but this situation could be changed by the discovery of the nuclear receptors farnesol X and pregnane X.[1,2] These receptors detoxify xenobiotics by activating genes responsible for phase I, II, and III drug-metabolism reactions. Thus inducers of nuclear receptors could be used to relieve cholestasis, indeed, ursodeoxycholic acids and rifampicin are used clinically.[3–5] Recently, Stefano Fiorucci and colleagues[6] showed that a semi-synthetic inducer of the farnesol X receptor, 6-ethylchenodeoxycholic acid, reverses bile-flow impairment induced by oestradiol in rats. By contrast, ursodeoxycholic acid did not increase bile-acid metabolism in human beings.[7] In addition, a 12-year clinical trial found ursodeoxycholic acid was not effective for primary biliary cirrhosis.[8] These data indicate there is potential for developing stronger nuclear-receptor activators for better treatment of cholestasis.

The normal homoeostasis of bile acids is shown in the figure. Primary bile acids are made in the liver from cholesterol. Two important enzymes are cholesterol 7α-hydroxylase and sterol 12α-hydroxylase.[6,9] The bile acids are excreted through bile-acid transporters, such as bile-salt excretory pump, multidrug-resistance protein 3, and multidrug-resistance-associated protein 2, into the intestines.[10,11] Secondary bile acids are formed in the intestine by the bacterial 7α-dehydroxylation of cholic acid and chenodeoxycholic acids. Most of them are absorbed into blood and extracted by hepatocytes through Na^+-taurocholate-cotransporting polypeptide and Na^+-independent organic anion-transporting polypeptide 2 to begin enterohepatic circulation.[9,11]

The causes of cholestasis are diverse, including genetic defects in the bile-salt excretory pump, multidrug-resistance protein 3, or multidrug-resistance-associated protein 2 transporters, anatomical obstruction, and many drugs such as oestrogens, chlorpromazine, erythromycin, oxypenicillins, tamoxifen, and newer macrolides.[12,13] High concentrations of bile acids in cholestasis have detergent effects that are toxic.[14,15] In vitro in rat hepatic microsomes, all bile acids have non-specific inhibitory effects both on cytochrome P450 enzymes such as CYP2A1, CYP2C11, and CYP3A2 and on non-cytochrome-P450 enzymes such as steroid 17β-dehydrogenase and P450-reductase.[15] However, the CYP inhibitory potential of bile acids was inversely related to the extent of hydroxylation of the bile-salt molecules with lithocholic acid, the most hydrophobic being the most toxic.[15]

In the treatment of cholestasis, several drugs can reduce serum concentrations of bile acids, which is a major pathogenic factor. Thus the anion-exchange resin, cholestyramine, is used to increase faecal

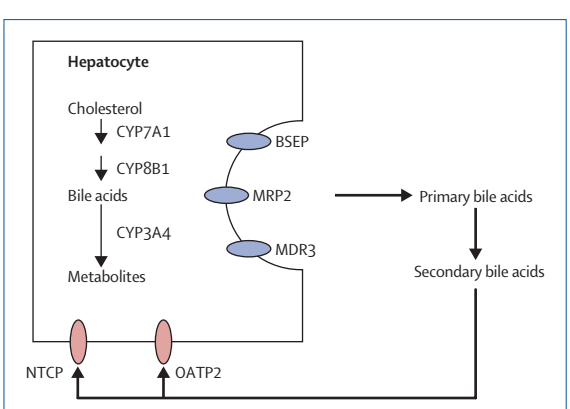

Figure: **Bile-acid homoeostasis and circulation**
Primary bile acids are biosynthesised from cholesterol by CYP7A1, CYP8B1, and other enzymes. They are detoxified by CYP3A4 into metabolites and transported into canaliculi by bile-salt-excretory pump (BSEP), multidrug-resistance protein 3 (MDR3), and multidrug-resistance-associated protein 2 (MRP2). Primary bile acids in intestines are converted into secondary bile acids and taken up by hepatocytes through Na^+-taurocholate cotransporting polypeptide (NTCP) and Na^+-independent organic anion-transporting polypeptide 2 (OATP2) so they enter enterohepatic circulation.