but this ignores the fact that hydropic changes may be secondary, and that a hydatidiform mole can be retained for long periods without discharge, and also without any cellular reaction.

Dr. Hellmann may deserve gratitude for re-emphasising the possible role of immune reactions in spontaneous abortion, but much more evidence will be needed before this can be considered as the main action of thalidomide.

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SIR,—Mr. Bore and Professor Scothorne (June 4) seek to test experimentally the theory that thalidomide by an immunosuppressive action may have saved some congenitally malformed fœtuses from being aborted.[1] The crucial question, as has been pointed out,[1] in the acceptance of such a theory is proof that early spontaneous abortion is in fact a form of homograft rejection. Mr. Bore and Professor Scothorne examined this theory in the rabbit, the only laboratory animal where thalidomide is known to be unequivocally teratogenic, by observing whether thalidomide prolonged homograft survival and whether they could obtain malformed fœtuses.

There is little enough evidence that early spontaneous abortion is a form of homograft rejection. There is none that resorption (which may be the equivalent in the rabbit) is produced by such a mechanism. Hence whether thalidomide is or is not immunosuppressive in the rabbit is only of dubious relevance to the problem of its presumed teratogenic action in man. There is indirect evidence, however, that thalidomide may in fact have an immunosuppressant action in man. Several workers [2–5] have suggested that an autoimmune mechanism may be involved in lepromatous leprosy, and Matthews and Trautman have also obtained encouraging clinical results in treating lepra reactions with immunosuppressant drugs. It is particularly interesting therefore that in six patients suffering from lepra reactions in whom thalidomide was given as a sedative excellent objective and subjective improvement was obtained.[6]

Evidence of direct teratogenic action would be valuable in establishing that thalidomide did in fact cause the malformations which have been attributed to it, and such evidence has been sought in the chick embryo. While de Bock and Peters [7] and also Kemper [8] found thalidomide to be teratogenic, Carter [9] in a very large and carefully controlled study found that thalidomide produced no greater incidence of malformations than talc.

Even if the mechanism of early spontaneous abortion in man and resorption in the rabbit were identical, which is highly problematical, it is not possible to evaluate the teratological experiments of Mr. Bore and Professor Scothorne, since they omit essential details of technique and results. It has been stressed [10] that the route of administration of thalidomide is important, but they give no information on this point. It is probable that they gave the drug intraperitoneally, since they investigated the immunosuppressive effects by the same route; they found "typical" thalidomide malformations, including phocomelias, but if in fact the drug was given by this route then their results conflict with the findings of others [11] who have been unable to obtain malformations when thalidomide was given in this way. Virtually all other workers have obtained their teratogenic effects in the rabbit when they gave thalidomide orally. Furthermore, the claim of Mr. Bore and Professor Scothorne to have obtained phocomelias stands in contrast to the findings of Fratta et al.[12] who, after careful large-scale experiments, came to the conclusion that "severe defects like phocomelia . . . cannot be produced in rabbits", and their opinion appears to be shared by all other investigators.

Since they give no numerical data it is not clear, moreover, whether the number and type of malformations Mr. Bore and Professor Scothorne obtained differed significantly from those in their controls—indeed, it is not even clear whether they included a control group in their experiments. It is difficult to accept therefore that they have satisfactorily answered the question which they have posed themselves—namely, does thalidomide produce fœtal abnormalities in the type of rabbit used in their grafting experiments? Consequently their claim to have invalidated the theory they set out to examine remains unproven.

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CERVICAL SPONDYLITIS AND VERTIGO

SIR,—I have read with considerable interest the letter from Dr. Hargrave-Wilson and Dr. Sherrey (June 4). In recent lectures to general practitioners on a course of instruction organised by this association, Professor Jack Joseph has stated that nipping of the vertebral artery on head rotation is practically impossible without gross arthritic bony changes at the atlanto-axial joints. Obviously the point Dr. Hargrave-Wilson and Dr. Sherrey raise requires elucidation, and it seems that only vertebral arteriography will answer the question whether arterial occlusion or cervical sympathetic irritation produces the vertigo associated with cervical spondylitis. We are pleased to have their confirmation that, as we have been teaching our postgraduate students, cervical manipulation relieves the symptoms in many of these cases.

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WARM KNEES AND COLD FEET

SIR,—I have been frequently assailed by visitors from England about the failure of many American investigators to cite European published work. I have noticed, however, that the reverse of this has been becoming an increasingly frequent occurrence in the articles published in your journal. May I therefore take the liberty of enclosing a reprint of an article from our laboratory which covers the topic of an article by Mr. Gaylis (April 9). The article cites no references, while it covers the same ground as the one published from our laboratory, and neither adds to nor subtracts from the previous publication.

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*** This letter was shown to Mr. Gaylis, whose reply follows.—ED. L.

SIR,—I am pleased to have had my attention drawn to the interesting article by Dr. Zweifler.[13] Unfortunately, I was not aware of his article at the time of preparation of mine—not that I failed to consult the published work, as implied by your correspondent, but because the reference was not available to me at the time. Dr. Zweifler's article appeared in February, 1965, and this was catalogued in the *Index Medicus* as late as December, 1965. This volume only arrived in our library at the end of January, 1966, by which time I had already completed my search for relevant references and the first draft of

my article. I hope that your correspondent will accept this explanation for the omission of this reference in my paper.

Dr. Zweifler makes the point that 3 of his patients with hot knees who were further investigated by arteriography or surgery revealed lower popliteal-artery occlusions, and it might be inferred from this that reconstructive surgery is thus not possible. My own experience, however, suggests that this may not be the case. In 7 of my patients, in whom the sign was "strongly positive", the distal segment of the popliteal or origin of either posterior or anterior tibial arteries was patent, thus making direct arterial surgery feasible. In fact, this was done in 5 patients with immediate failure in 1.

Warm zones are not only confined to the knee, but may be found on the antero-medial aspect of the thigh in the presence of a short segmental adductor hiatus occlusion. The zone of increased warmth is not as pronounced as that found around the knee because the collaterals are situated on a deeper plane.

I hope that my short article, while obviously not "new", will help to evaluate this easily detectable clinical sign.

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PHYTOHÆMAGGLUTININ AND THYMIC LYMPHOCYTES

SIR,—In suggesting that thymus cells respond to phytohæmagglutinin (P.H.A.) differently from lymphocytes from blood or lymph-gland, Dr. McIntyre and Mr. Segel (June 4) refer to our article [1] in which we described the technique of leucocyte cultures obtained from thymus and spleen post mortem. The purpose of our article was the establishment of a method and of the practicability of this method for obtaining metaphase preparations for karyotyping; we were not primarily concerned with the role of P.H.A. Although it was not mentioned, we had in fact carried out controls without P.H.A. and found that after 72 hours' incubation there was no wave of mitosis. Cultures incubated for 7 days without P.H.A., while sometimes yielding a few cells in mitoses, did not yield the number of mitoses required for karyotyping. We doubt the relevance of a comparison between observations based on the culture of thymus taken post mortem from the newborn with those obtained from cultures of the involuting thymus of older subjects.

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RIB ABSENCE IN DOWN'S SYNDROME

SIR,—Dr. Beber [2] has postulated that in some patients with Down's syndrome there may be a developmental error of the 12th thoracic vertebra due to failure of the appropriate sclerotome to form. He based this hypothesis on a report of 2 boys and 9 girls, among 36 patients who had 11 instead of 12 ribs. Dr. Thuline and Dr. Islam (May 21) have surveyed 251 patients and found an excess of the missing-rib anomaly among female patients (29 compared with 21 males).

We have examined penetrated chest X-rays of 162 patients: 91 males (age-range 8–60 years), and 71 females (age-range 7–54 years). The distribution of rib anomalies was as follows:

Rib anomaly	*Males*	*Females*	*Combined*
Normal number of ribs and thoracic vertebræ	85	47	132
12th rib absent on right side only	0	4	4
12th rib absent on left side only	2	1	3
Both 12th ribs absent but 12th thoracic vertebra present	0	3	3
Both 12th ribs absent (11 thoracic vertebræ only)	4	16	20
Totals	91	71	162

All but 8 of the patients had a regular 21-trisomy anomaly. Details of the 8 patients with irregular chromosome anomalies were as follows:

Chromosomal anomaly (and sex)	*Rib anomaly*
46/47 mosaicism (M)	Ribs and vertebræ normal
13/21 translocation (M)	" " " "
46/47 mosaicism (M)	" " " "
21/22 translocation (M)	Both 12th ribs missing and absent 12th thoracic vertebra
46/47 mosaicism (F)	Both 12th ribs missing and absent 12th thoracic vertebra
13/14 translocation (F)	Normal number of ribs and vertebræ " " " " " "

These observations confirm Dr. Thuline and Dr. Islam's finding of a significant increase in the number of females showing the absent-rib defect compared with males. The sex difference for absence of ribs or for absence of the 12th thoracic vertebra is significant beyond the 0·01 level of confidence on a χ^2 test with one degree of freedom. Absence of the 12th thoracic vertebra associated with bilateral absence of the 12th rib conforms with Dr. Beber's suggestion that this defect may be the result of an absent sclerotome.

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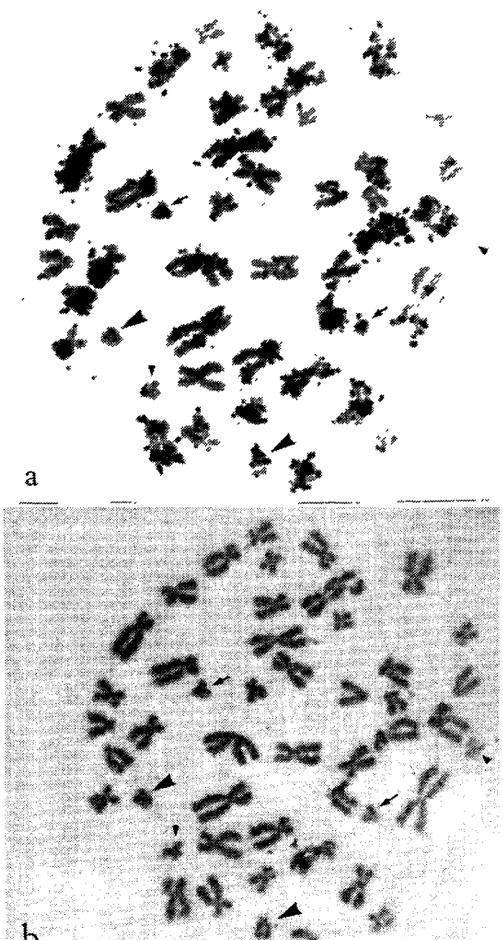
YY SYNDROME WITH MULTIPLE MALFORMATIONS

SIR,—Two Y chromosomes have been found in males with high stature, high-grade mental deficiency or below-average intelligence, and aggressive behaviour by Dr. Price and his colleagues (March 12). No consistent physical features or characteristic malformations have been seen in XYY individuals reported so far. Among these the patient of Hustinx and



Metaphase chromosomes of leucocyte stimulated by phytohæmagglutinin, showing asynchronous replication of the two Y chromosomes after incorporation of ^{3}H-thymidine (a), and with silver grains removed (b).

Large arrow-heads point to Y, stalked arrows to G_1, and small arrow-heads to G_2 chromosomes.

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