do not know whether it is due to the effects of toxic compounds or whether it is a genetic association. Whether dietary manipulation will affect the development of obstructive cardiomyopathy remains to be seen; if it does, diagnosis would need to be made early in life. Whatever the aetiology of the cardiomyopathy, the association with tyrosinaemia suggests that caution should be exercised in counselling parents about prognosis for this disorder, particularly with regard to liver transplantation, which may not then be the curative approach that some have suggested.4

MARY ANNE EDWARDS
ANNE GREEN
A. COLLI
G. RYLANE

SEROLOGICAL RESPONSE TO HEPATITIS DELTA VIRUS IN HEPATITIS D

Sir,—We essentially agree with Dr Aragona and colleagues (Feb 28, p 478) about the serological response to delta hepatitis. We also find that in self-limited coinfections of hepatitis B virus (HBV) and hepatitis delta virus (HDV), antibody responses, particularly IgM, are short-lived. The humoral response to self-limited HBV/HDV coinfections may appear delayed in relation to the onset of illness because initial symptoms may reflect infection with HBV rather than HDV. This is most obvious in those cases having a typical “biphasic” course,1,2 where symptomatic acute hepatitis rises progressively to levels associated with chronic delta hepatitis. This is usually much higher in chronic than acute HDV infection, and following acute HDV superinfection of an HBV carrier, usually rises progressively to levels associated with chronic delta hepatitis. Those rare cases of superinfection that are followed by clearance of both viruses1 do not produce the strong IgG anti-HDV response seen in chronic HDV infection. We believe, therefore, that patterns of IgG anti-HDV following coinfection or superinfection are also of diagnostic benefit. How long IgG anti-HDV persists after self-limited delta hepatitis remains to be clarified.

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DOES “CENTRAL” OBESITY PREDICT CORONARY ARTERY DISEASE?

Sir,—Dr Donahue and colleagues (April 11, p 821) have studied the relation between subscapular skinfold thickness and coronary heart disease (CHD) in men of Japanese ancestry in Hawaii. They describe subcapsular fat as “central” fat and claim that it is independently related to serum cholesterol, serum triglycerides, hypertension, and so on. We find that skinfold thickness at any one of the four commonly measured sites is equally related, quintile by quintile, to serum cholesterol, triglycerides, and systolic and diastolic blood pressure. The thickness of the triceps subcutaneous, iliac, and abdominal skinfolds equal summed skinfolds as predictors of lipid levels, triglycerides, or blood pressure. The thickness of the triceps skinfold and the fat-shadow measurement on chest X-rays were both linearly related to 11 year and 16 year cardiovascular mortality in Scotland.1 Although different fat deposits have been variously categorised as peripheral/central, upper-body/lower-body, or centrifugal/centripetal, it is by no means certain that differences in anatomical location are functionally important. Skinfold/skinfold intercorrelations are all high, averaging 0·75 in adult males and 0·82 in women aged 20–49, and the individual correlations with lipids or blood pressure are not meaningfully different with or without age adjustment. Thus, we do not agree with Donahue et al that the subscapular skinfold has unique predictive powers or that partial correlations allow us to ascribe which skinfold of the four best reflects the illness-causing aspects of fatness. We agree that fatter individuals are more likely to experience cardiovascular accidents such as coronary occlusions or stroke, even after partitioning for cigarette smoking. We also agree that measurements of subcutaneous (ie, “outer”) fat are superior to

<table>
<thead>
<tr>
<th>Skinfold quintile</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total cholesterol (mg/dl)</strong></td>
<td>207</td>
<td>215</td>
<td>220</td>
<td>228</td>
<td>229</td>
</tr>
<tr>
<td>Triceps</td>
<td>199</td>
<td>213</td>
<td>223</td>
<td>230</td>
<td>235</td>
</tr>
<tr>
<td>Subscapular</td>
<td>203</td>
<td>212</td>
<td>226</td>
<td>227</td>
<td>229</td>
</tr>
<tr>
<td>Iliac</td>
<td>201</td>
<td>213</td>
<td>229</td>
<td>235</td>
<td>230</td>
</tr>
<tr>
<td>Abdominal</td>
<td>205</td>
<td>216</td>
<td>218</td>
<td>228</td>
<td>231</td>
</tr>
<tr>
<td><strong>Diastolic BP (mm Hg)</strong></td>
<td>78</td>
<td>81</td>
<td>81</td>
<td>83</td>
<td>86</td>
</tr>
<tr>
<td>Triceps</td>
<td>78</td>
<td>80</td>
<td>83</td>
<td>84</td>
<td>88</td>
</tr>
<tr>
<td>Subscapular</td>
<td>78</td>
<td>81</td>
<td>82</td>
<td>83</td>
<td>87</td>
</tr>
<tr>
<td>Iliac</td>
<td>77</td>
<td>80</td>
<td>83</td>
<td>87</td>
<td>87</td>
</tr>
<tr>
<td>Abdominal</td>
<td>78</td>
<td>80</td>
<td>81</td>
<td>83</td>
<td>87</td>
</tr>
</tbody>
</table>

Source: Tecumseh, Michigan, Community Health Survey Examination, round 2.
Recognise the transformed cells. Priming of macrophages, however, and thereby prime macrophages. This suggests that T cells still tumour cells) upon stimulation with interferon-γ the results of these (unpublished). High neopterin levels indicated a poor prognosis. The association between neopterin and prognosis in patients with certain malignant diseases, a high frequency of raised or active autoimmune disorders support the concept that neopterin secreted from macrophages after stimulation by interferon-γ.3 In vitro, neopterin is tumours, seem to be consistent with this view. In vitro, neopterin is predictive. Moreover the subcapsular skinfold does not necessarily behave like trunk fat over the entire fatness range. At higher levels of fatness, the subcapsular skinfold decreases in its relative contribution to the summed skinfold total while the iliac and abdominal skinfolds become an increasing part of the total (figure).

Changing relative contributions of four different skinfolds to summed skinfold total in men.

Subcapsular skinfold behaves more like "peripheral" skinfold and less like skinfolds of trunk.

weight-for-height indices in their relationships to other risk factors.2 However, we do not agree that the subcapsular skinfold is uniquely predictive. Moreover the subcapsular skinfold does not necessarily behave like trunk fat over the entire fatness range. At higher levels of fatness, the subcapsular skinfold decreases in its relative contribution to the summed skinfold total while the iliac and abdominal skinfolds become an increasing part of the total (figure).

SUBCAPSULAR

ILIAC

ABDOMINAL

THigh

SCap

Subscapular

summed skinfold total in men.

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ACTIVATED MACROPHAGES AND CANCER

Sir,—Dr Munzarova and Dr Kovarik (April 25, p 952) present the hypothesis that activated macrophages help both the establishment of tumours and metastasis by the secretion of substances that favour cell growth and angiogenesis and by their ability to fuse with malignant cells. This view contradicts the simple concept of immune surveillance whereby activation of components of the immune system is invariably beneficial to the host of a tumour. In principle, however, the interaction of activated macrophages with tumour cells can either inhibit or promote tumour growth, depending on the cytokotic function of the macrophage or the capacity of these cells to stimulate cell proliferation and/or angiogenesis.1,2 Since metastatic spread is usually responsible for fatal outcome in malignant disease, the proposed role of macrophages for enhancement of metastasis, possibly by fusion with transformed cells, might be crucial for prognosis.

Raised neopterin levels, observed in patients with malignant tumours, seem to be consistent with this view. In vitro, neopterin is secreted from macrophages after stimulation by interferon-γ.3

Investigations in, for example, patients with graft rejection episodes or active autoimmune disorders support the concept that neopterin is a marker for activation of the T lymphocyte/macrophage axis. In patients with certain malignant diseases, a high frequency of raised neopterin levels has been found.4 We and others have investigated the association between neopterin and prognosis in patients with carcinomas of the uterine cervix,4 lung,6 prostate,7 and ovary (unpublished). High neopterin levels indicated a poor prognosis.

As neopterin is produced specifically by macrophages (and not by tumour cells) upon stimulation with interferon-γ the results of these studies indicate that T cells in cancer patients release interferon-γ and thereby prime macrophages. This suggests that T cells still recognise the transformed cells. Priming of macrophages, however, cannot be equated with the killing function of these cells. Rather, the inability of the immune system to clear the organism from the tumour indicates that there might be a failure in the subsequent killing of transformed cells by macrophages and cytotoxic T cells.

Whether macrophages are directly involved in establishing malignant tumour cannot be concluded from our results. The data, however, do indicate the presence of macrophages stimulated by interferon-γ in patients with certain cancers and suggest that the presence of these cells is associated with poor prognosis.


SIR,—Dr Munzarova and Dr Kovarik’s hypothesis on a role for macrophage-mediated cell fusion in metastasis may prove as provocatively useful as it is self-confessedly audacious.

The specific example of malignant melanoma apart, it is interesting to consider the relevance of macrophage-mediated cell fusion to foreign body tumorigenesis, such as that produced by exposure to non-biodegradable materials. In vivo experiments with mineral fibres1 and tissue culture studies of the effects of asbestos on Chinese hamster cell lines2 and on pleural tissue explants3 have revealed many karyotypic and chromosomal abnormalities, including polyploidy and macronuclei. In vivo4 and in vitro5 studies have also indicated the importance of fibre morphology and dimensions, fibres longer than about 7 μm and thinner than about 1-5 μm being both more carcinogenic and more cytotoxic to lung cells in culture. Microcinematographic examination of a mouse-derived macrophage-like cell line treated with asbestos in culture4 has indicated that cells attached to partly phagocytosed long asbestos fibres may still be viable and undergo mitosis. Similarly, morphological and ultrastructural investigations of cultured primary mouse macrophage cells exposed to asbestos utilising scanning and transmission electron microscopy6 has revealed that long asbestos fibres may be associated with several macrophages juxtaposed along its shaft, a feature indicative of partial endocytosis ("frustrated phagocytosis"). Pleural mesothelial cells in culture also exhibit phagocytic activity on exposure to asbestos fibres.8

Evidence for in vivo cell fusion in human malignant tumours has been presented,9 and the finding of giant cells in cultured alveolar epithelial cell lines exposed to asbestos10 has led to the suggestion that they are formed by cell fusion. Whilst cell fusion may be induced by a variety of viral and chemical agents, of special significance to fibre-rela ted tumorigenesis is the production of fused hybrid mammalian somatic cells by microneedle surgical stimulation.11 Perhaps asbestos fibres have a comparable role in facilitating the cellular fusion of phagocytic cells (macrophages and mesothelial cells) with other, possibly neoplastic, cells, hence contributing to malignant transformation and tumour formation. Such synergism may provide a cellular mechanism for the tumour-promoting properties of mineral fibre particles, as