patient's discharge and therefore is a source of morbidity.

It has been our practice in Rochdale to have a running total of wound infections. However, unless this sort of survey is personally supervised the results are likely to be grossly inaccurate as was found to be the case in our hospitals. It is of interest to note that the corrected infection rate in our wounds was 5% in clean wounds and 27% in potentially infected wounds, compared with the Aberdeen figures of 5.4% and 19.7%, respectively. However, only one of our three wards surveyed is subdivided, the others being of Nightingale type, and none has positive-pressure ventilation, the addition of which would undoubtedly be associated with improvement, as was noted from the published series.

In conclusion I would like to make a plea that infection surveys be carried out routinely in peripheral hospitals; the survey must be personally supervised by a consultant (pathologist or surgeon) and is likely to be more effective if performed for a short intensive period rather than a routine affair. The active help and encouragement of the nursing staff and the junior hospital doctors must be sought. Most peripheral hospitals have not the facilities which are available in Aberdeen but this should not preclude meaningful assessment of performance.—I am, etc.,

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Abnormal Bile or Faulty Gall Bladder?

SIR,—I enjoyed reading your leading article on the aetiology of gallstones (5 December, p. 571). You rightly quoted the important study of Small and Rapo which showed that in patients with cholesterol gallstones the bile is already overloaded with cholesterol when secreted by the liver.¹ Essentially the same findings were reported at about the same time and quite independently by Vlahcevic, Bell, and Swell.² Moreover, these workers have gone on to make the important new observation that patients with gallstones have an abnormally small bile-salt pool.³ If confirmed, this finding will strengthen the case for the "abnormal bile" origin of gallstones and provide a mechanism for the poor cholesterol-holding capacity of bile.

The fundamental question, which is not answered by these studies, is "Why does the liver secrete abnormal bile?" Two answers are possible: (1) the liver itself is faulty, and (2) the liver is forced to work faultily by outside influences. The editor of another journal has expressed his opinion in a leading article entitled "Gallstones—a new liver disease?"⁴ In so doing he has prejudged the issue and in effect dismissed the possibility that the liver is abnormal in the sense only that it is responding, quite innocently, to abnormal external influences. Your own leading article also omits any reference to external factors, perhaps in the cause of brevity.

I suggest, however, that it is through the study of external—that is, environmental—factors that the cause of gallstones will be

found rather than through studies of the liver or the gallbladder. There is good epidemiological evidence for this belief. At a special meeting on gallstones in Copenhagen in July 1970 (during the 4th World Congress of Gastroenterology) Dr. Nakayama described how in Japan cholesterol gallstones have become much commoner in the last 40 to 50 years—that is, during the period of increasing Western-style affluence. This report confirmed the trend away from pigment stones and towards cholesterol stones which was first noted in city dwellers and people of the higher social classes.^{5,6} At the same meeting several European experts agreed that during the last war cholesterol gallstones became less common, at least as a clinical problem. Recently there has been a report of increased incidence of gallstones in Italians who emigrate to Australia,⁷ while in affluent Sweden gallstone incidence has risen to unprecedented levels in the last one or two decades.⁸

All these data point to an environmental cause, associated with the modern Western way of life. A dietary cause seems most likely, both on logical grounds and because of the association between cholelithiasis and obesity.⁹ Indeed, Sarles has produced good evidence of excessive calorie intake in gallstone patients¹⁰ (though some other workers do not agree). Further work in this field is urgently needed but meanwhile it is worth noting the observation made almost 80 years ago by that astute clinician William Osler: "The subjects (having gallstones) are often stout, and usually very fond of starchy and saccharine food".¹¹

It is more convenient to study organs and body fluids than whole people and their way of life but I believe it is the latter which hold the key to the gallstone mystery.—I am, etc.

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Resuscitation Too Late

SIR,—Since I retired I have seen with alarm the treatment of some aged relations and friends—for example,

A confused but happy lady, aged 90, cared for by her daughter in a nursing home, having fallen out of bed was sent to hospital to be "pinned." Acute dyspnoea after operation was not treated, apparently for fear she might succumb from effects of drugs. When she died on the fourth day the house surgeon applied external cardiac massage. The daughter, a State-registered nurse who was present, asked that she

should be left in peace. The reply was "I have my duty to do."

A lady of 89, nearly blind with glaucoma and unhappy in living with a son-in-law she disliked, having been "saved" from pneumonia almost annually by antibiotics, was found to have an enormous cervical carcinoma. She was sent many miles from all her relations to a hospital where the nursing was of the very best but where radiotherapy did nothing but make her sick and was abandoned. In a hospital nearer home her catheter was removed, and she was allowed to remain 36 hours in great pain while the house physician mumbled about infection and antibiotics. Now she is at home where her merciful doctor is using morphine.

You have my name. I look forward to my own old age as ever with distaste, but now with dread.—I am, etc.,

CONSULTANT PHYSICIAN
(retired in 1969)

Indications for Hysterectomy

SIR,—During the past two years 30 out of a total of 1,264 new patients referred to my general surgical outpatient clinics have previously had abdominal hysterectomy. Pathological examinations of the operation specimens in these 30 cases showed that in 12 no abnormality of the pelvic organs was found. In the remaining 18 the following lesions were present: Endometrial or cervical polyps 7; carcinoma of cervix 5; fibroid uteri 3; ovarian cyst 2; endometriosis 1. The operations have been performed in several hospitals, mostly in N.E. England. In this group of patients, therefore, no pathological lesion was present in 40% of them, and in a further 23% lesions (polyps) which could have been dealt with by conservative surgery were present. In 27% of the cases pathological processes which could not have been removed except by major surgery had been demonstrated. These figures suggest there has been a shift in the indications for abdominal hysterectomy and it would be of interest to know if they represent a typical sample.—I am, etc.,

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Metformin and Stanozolol in Blood Fibrinolytic Activity

SIR,—We have previously reported that a combination of phenformin and stanozolol increases the fibrinolytic activity in the blood.^{1,2} We have used this treatment for patients with cutaneous vasculitis, Behçets syndrome, and recurrent deep vein thrombosis where the fibrinolytic activity was reduced, and found that it not only increased this activity but produced clinically beneficial results.^{2,3,4}

We have now investigated whether the same effects could be obtained by the administration of a combination of metformin (Glucophage) and stanozolol. Blood fibrinolytic activity was estimated by the euglobulin lysis time (E.L.T.) method using an E.L.T. recorder.⁵ Twenty patients divided into two groups of ten each were investigated.

Group 1.—This group consisted of three patients suffering from recurrent deep vein thrombosis and seven patients who had suffered a myocardial infarction with decreased fibrinolytic activity who were treated with phenformin

(50 mg twice daily) and stanozolol (5 mg daily). They had been on this treatment for 24 weeks with increasing improvement in their fibrinolytic activity. It was decided to switch them to metformin (850 mg thrice daily) and stanozolol (5 mg daily) and to estimate the blood fibrinolytic activity at four weekly intervals. At the time of writing they have been studied for 32 weeks.

Group 2.—This group included ten patients with decreased fibrinolytic activity who had suffered a myocardial infarction three to four months prior to the study and in whom the anticoagulant therapy was being tailed off. Before initiating the new treatment their blood fibrinolytic activity was estimated. Subsequently a combination of metformin (850 mg thrice daily) and

TABLE I—Last Estimates on 10 Patients when Treated with Phenformin and Stanozolol Compared with Estimations of Euglobulin Lysis Time (in units) at 4 and 32 week period when Treated with Metformin and Stanozolol

	Phenformin + Stanozolol	Metformin + Stanozolol	
		At End of Week 4	At End of Week 32
Mean	93.0	92.6	93.6
S.D.	21.27	42.7	22.7
Mean Difference		-0.4	+0.6
		>0.9	>0.9
		Not significant	Not significant

stanozolol (5 mg daily) was administered, and the blood fibrinolytic activity estimated at four weekly intervals. The study of this group has so far been in progress for 40 weeks.

The increased blood fibrinolytic activity observed in the ten patients on phenformin-stanozolol was maintained when this was replaced by metformin-stanozolol (Table I). There was no significant difference between the effect of the two drug combinations on the blood fibrinolytic activity ($P>0.9$). The blood fibrinolytic activity was significantly higher after metformin-stanozolol therapy in group 2 ($P<0.001$), and this increase which could be observed already at the end of four weeks' treatment was still present at the end of 40 weeks (Table II).

TABLE II—Euglobulin Lysis Times (in Units) Before and During Treatment with Metformin and Stanozolol: Comparison Between "Before Treatment Estimations" and "Estimations at Different Time Period"

	Before Treatment	At End of Week 4	At End of Week 40
Mean	32.4	97.4	100.6
S.D.	18.32	35.22	21.44
Mean Difference from Before Treatment		+65.0	+68.2
S.E. of Difference		13.1	10.2
P		<0.001	<0.001

This pilot study indicates that the combination of metformin-stanozolol is as effective in increasing the blood fibrinolytic activity as that of phenformin-stanozolol.—I am, etc.,

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Mechanisms in Pernicious Anaemia

SIR,—We were interested in a number of points raised by your leading article "Mechanisms in Pernicious Anaemia" (26 December, p. 757) but particularly in your statement that "vitamin B₁₂ released from food . . . becomes bound to intrinsic factor." Could you please tell us where one can find published evidence that this release and subsequent binding of the vitamin to intrinsic factor actually occurs in the stomach? We have asked this question on other occasions but have never received a reply to it.¹⁻³

On the other hand, some years ago, we published evidence⁴ that free vitamin B₁₂ is not present in appreciable amounts during gastric digestion and is, therefore, not available to combine with "intrinsic factor" or anything else in the stomach. In the same communication we showed that protein bound to vitamin B₁₂ is digested like any other protein and that the vitamin is released in a progressive and logical manner under the influence of the alimentary proteases. This release occurs, as one might expect, simultaneously with the release of α amino nitrogen. There is no evidence that vitamin B₁₂, when once released binds itself again to any large molecule during digestion. As far as we are aware these findings have not been challenged.

We do not believe that the absorption of vitamin B₁₂ is one of "Nature's mysteries" as you suggest. Rather do we think it to be a man-made mystery based upon the myth of "intrinsic factor."—We are, etc.,

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SIR,—Your leader on "Mechanisms in Pernicious Anaemia" (26 December, p. 757) ends on the challenging note that "we need to define more precisely the biochemical basis underlying megaloblastic erythropoiesis." I believe that sufficient basic principles have been established to give us some insight as to what may be happening—although not necessarily all that is happening—within the DNA molecule of the megaloblast nucleus.^{1,2}

If we accept three well-authenticated hypotheses certain conclusions can be drawn which point to an interesting biological lesion in the megaloblast. The first of these is the Watson-Crick hypothesis of the double helical structure of the DNA molecule and its control of protein synthesis.³ The second concerns the mode of action of folic acid and vitamin B₁₂. The former in the form of 5-10 methylenetetrahydrofolic acid is concerned with the methylation of deoxyuridylic acid to form thymidylic acid, being itself reduced to dihydrofolic acid. Vitamin B₁₂ is concerned in the demethylation of 5-methyltetrahydrofolic acid—an essential step in the regeneration of the 5-10 methylene derivative—the methyl group being transferred to homocysteine to form methionine.⁴ In vitamin-B₁₂ deficiency 5-methyltetrahydrofolic acid may accumulate in the tissues,⁴ and the serum methionine level is lowered in both B₁₂ and folic acid deficiency.⁵ Both folic acid and

vitamin B₁₂ are therefore directly or indirectly concerned with the methylation of deoxyuridylic acid to form thymidylic acid.

Finally, there is the inevitable conclusion that, as far as the marrow is concerned, megaloblastosis is always—except in one or two exceptionally rare conditions such as oroticaciduria—a manifestation of a deficiency state, a deficiency of either vitamin B₁₂ or of folic acid and, in view of the action of these, ultimately a deficiency of thymidylic acid (T). An important corollary of the last hypothesis is that at the onset of the deficiency the cells themselves are normal.

We can therefore consider a hypothetical state where a normal cell is exposed to a state of complete T deficiency. This impairs DNA replication, and therefore mitosis, but leaves RNA and protein synthesis intact² (Fig.)

C=deoxycytidylic acid
G=deoxyguanylic acid
A=deoxyadenylic acid
T=deoxythymidylic acid
U=uridylic acid

Underlined capitals corresponding ribonucleic acids

This is consistent with the greatly raised RNA/DNA^{6,7} and uracil/thymine⁷ ratios reported in megaloblastic marrows as well as with the two main haematological features of megaloblastic anaemias, namely, a deficiency in number of red cells and, in the absence of iron deficiency, a normal mean corpuscular haemoglobin concentration.

In practice, however, the deficiency of neither B₁₂ nor of folic acid is ever complete and the cells are not therefore exposed to a state of complete T deficiency. The varying degree of maturity of individual megaloblasts could, however, possibly be explained by a varying degree of thymidylic acid deficiency in each cell. The degree of thymidylic acid deficiency could be so severe as to completely prevent replication and probably end in cell death (ineffective erythropoiesis), whereas other cells enjoy a full complement of thymidylic acid, as shown by the occasional presence of normoblasts—in other words, normal cells in megaloblastic marrows. In between these extremes the deficiency of thymidylic acid could be of a degree that would considerably retard the process of replication. This could result in single-strand breaks in the DNA molecule, which could well explain the characteristic morphology of the megaloblast nucleus. Such single-strand breaks can be produced experimentally by deoxyribonuclease in