Conclusions

Our experience with peritoneoscopy leads us to believe that it is a safe, and minor, procedure which, if employed with due regard to its limitations, will give information that could otherwise be obtained only by laparotomy.

Obesity and abdominal adhesions are contraindications to peritoneoscopy because no useful information is likely to be obtained. Peritoneoscopy is unnecessary if the patient certainly needs an operation for treatment, but it may indicate the necessity for operation when this is in doubt.

Peritoneoscopy is most successful in the diagnosis of liver disease, ascites, and abdominal masses, and in estimating the spread of abdominal malignant disease. When employed for a definite indication peritoneoscopy achieves its purpose in nearly 90% of technically successful cases. Peritoneoscopic biopsy has been used in very few of our cases, but its value is unquestioned. We shall continue to use it with caution because of its dangers.

Summary

The results of peritoneoscopy in 136 patients are reported. There was no mortality, and only minor complications were encountered.

In 79.4% of all cases, and in nearly 90% of the technically successful examinations, useful diagnostic information was obtained by peritoneoscopy.

Peritoneoscopy has its chief value in diagnosing the nature of hepatomegaly and ascites. In suitable cases it saves the need for laparotomy, and is much safer, more comfortable, and more rapid, both in performance and in recovery of the patient.

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The National Old People's Welfare Council's *Progress Report* for the year ending March 31, 1956, records a satisfactory year. The various organizations which form the council have continued to co-operate to help the elderly, and the public has become more aware of the problem. The number of letters asking for information has increased, and the press and B.B.C. are constantly passing on to the council the inquiries they receive about elderly people. When these inquiries are frequently on the same subject the council prepares a special memorandum giving basic information. During the year a memorandum on the night attendance, home bathing, evening visiting, and laundry services for the elderly has been prepared; those on housing and chiropody have been revised. The *Progress Report* includes a list of the council's publications and their price. Boarding-out information is included in the quarterly *Bulletin*, which has now reached a distribution of 15,730. The number of local Old People's Welfare Committees is 1,205, and the whole country is covered by them on an area, regional, county, or local basis. There are now 5,000 clubs throughout the country, and no lonely elderly person need be without a friendly caller if he or she so wishes. The *Report* also includes a financial statement, list of represented organizations, and addresses of county committees. There is also a form of bequest for those who might wish to contribute. The *Report* is obtainable from the council, 26, Bedford Square, London, W.C.1, price 1s. 6d.

NEODYMIUM 3-SULPHO-ISONICOTINATE AND BLOOD COAGULATION

BY

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It has been known since 1930 that some of the rare earth metals affect blood coagulation both *in vitro* and *in vivo* (Guidi, 1930). Salts of lanthanum, cerium, praseodymium, and neodymium were found to prolong the clotting-time of whole blood on intravenous injection in animals, and to have an irreversible anticoagulant effect *in vitro* on whole blood and recalcified plasma (Dyckerhoff and Kuerten, 1936; Dyckerhoff *et al.*, 1936; Vincke and Oelkers, 1937). All the compounds used were very toxic until Vincke (1947) reported that neodymium nicotinate could be given to animals in sufficient dosage to prolong the clotting-time of whole blood without toxic effects. It was later found (Vincke and Sucker, 1950) that neodymium 3-sulpho-isonicotinate was water-soluble, neutral, and could be sterilized in ampoules; its toxicity in cats was low; and it prolonged the clotting-time of whole blood in rabbits in a dose of 50 mg. per kg.; the full effect did not become evident for six hours, and lasted for 18–24 hours. It was claimed by these workers that this compound acts by interfering with circulating prothrombin and that it may also, in very high doses, precipitate fibrinogen. The newer knowledge and improved techniques in the study of blood coagulation have enabled us to examine afresh the mode of action of neodymium 3-sulpho-isonicotinate.

Experiments

We have confirmed the observation that the compound administered intravenously to dogs, rabbits, and mice in a dose of 50 mg. per kg. greatly prolongs the clotting-time of whole blood. It also prevented coagulation when added to blood immediately on withdrawal, so that it is active both *in vitro* and *in vivo*. Intravenous injection of protamine sulphate failed to restore the clotting-time to normal in neodymium-treated animals, and the addition of thrombin in various concentrations to various dilutions of normal and neodymium-treated plasmas gave similar results. The drug, therefore, does not interfere with the thrombin-fibrinogen reaction.

In all these experiments, in spite of a great prolongation of the whole blood clotting-time, the one-stage "prothrombin" time (Quick test) showed only a moderate prolongation of 6–12 seconds, and prothrombin measured by the two-stage test (Biggs and Douglas, 1953a) was normal. The most striking abnormality was in the generation of intrinsic blood thromboplastin (Biggs and Douglas, 1953b), which was grossly impaired in the treated animals, the deficiency affecting both the plasma factor (antihaemophilic globulin) and the serum factors concerned in the reaction.

A dose of 50 mg. per kg. is far too high to be either practicable or safe for human use, and in clinical studies we gave doses that had been reported from Germany as having favourable clinical results—namely, 250–375 mg. by intravenous injection. The results were consistent, and in some important respects quite different from the results obtained in animals with much larger doses. In all instances (more than 50 injections) the clotting-time of whole blood remained normal. Once again the thrombin-fibrinogen reaction was unimpaired.

The clotting-time of the oxalated plasma in the Quick test showed a variable prolongation of 0-14 seconds over normal, and this abnormality was corrected by the addition of one part in ten of aged normal serum, indicating a deficiency of factor VII (stable factor). The two-stage prothrombin measurements were within normal limits. Once again the most striking and consistent abnormality was impairment of intrinsic blood thromboplastin generation, but in these human studies, using a much smaller dose, the abnormality was found in the patient's serum only, the preparation containing antihaemophilic globulin (plasma treated with $\text{Al}(\text{OH})_3$ or Ba_2SO_4) behaving normally in the generating mixture. We then found that if rabbits were given a similar dose (5 mg. per kg.) the results were identical: no alteration in the clotting-time of whole blood, variable factor VII deficiency, and normal prothrombin, and a serum that was ineffective in generating thromboplastin from a mixture of platelet factor and normal adsorbed plasma. These effects were not always fully evident until three to four hours after injection, persisted for about 24 hours, and passed off within 36 hours. They were not prevented in humans by oral premedication with vitamin K_1 emulsion in 50-mg. doses.

FIG. 1.—Blood thromboplastin generated in a mixture with platelet factor and $\text{Al}(\text{OH})_3$ -treated plasma by the following sera: (1) normal serum; (2) Christmas disease serum 95% + neodymium serum 5%; (3) Christmas serum 90% + neodymium serum 10%; (4) Christmas serum 50% + neodymium serum 50%; (5) Christmas serum 30% + neodymium serum 70%; (6) Christmas serum 10% + neodymium serum 90%; (7) neodymium serum alone; (8) Christmas serum alone. 100% thromboplastin represents a clotting time in the substrate plasma of 10 seconds.

FIG. 2.—Blood thromboplastin generated in a mixture with platelet factor and $\text{Al}(\text{OH})_3$ -treated plasma by the following sera: (1) normal serum; (2) phenindione (P.I.D.) serum 90% + normal serum 10%; (3) P.I.D. serum 97.5% + neodymium serum 2.5%; (4) P.I.D. serum 95% + neodymium serum 5%; (5) neodymium serum alone; (6) P.I.D. serum alone.

done within a few minutes of withdrawal of the blood, but we found that the subsequent shortening of the one-stage clotting-time was never complete, a stable and still abnormal level being reached in about half an hour. Our other findings with oxalated plasma may be open to criticism on the grounds of this phenomenon, but it does not affect the difference between the results obtained with greatly different dosage, nor the abnormalities found in the serum of treated patients and animals. It is of interest that we found sodium citrate to be even more unsuitable as an anticoagulant for the study of neodymium-treated plasma, owing to the formation of a neodymium-citrate complex.

The patient of B. Alexander and R. Goldstein (1955, personal communication) with congenital factor VII deficiency generates thromboplastin normally, and there is additional evidence from the study of coumarin anticoagulants that this factor is not concerned in blood thromboplastin generation (Koller, 1953; Walker and Hunter, 1954). Once again, with neodymium, we found no correlation between factor VII deficiency and blood thromboplastin impairment.

Thromboplastin Generation

In order to establish which factor or factors in the serum were responsible for the impaired thromboplastin generation, a series of tests were done, using as the source of the thromboplastin constituents normally present in serum mixtures of normal serum, Christmas disease (P.T.C. deficient) serum, and serum from patients treated with phenindione or neodymium, in various combinations and proportions. The phenindione serum used was shown to have a satisfactory content of Christmas factor and, of factors necessary for thromboplastin formation, to be lacking only in factor X (Koller, 1953; Duckert *et al.*, 1955). It was found that mixtures of neodymium serum with Christmas serum, or with phenindione serum, resulted in mutual correction of impaired thromboplastin generation, but only if the concentration of neodymium serum was low—10% or below in the case of admixture with Christmas serum, and 2.5% in admixtures with phenindione serum (Figs. 1 and 2).

FIG. 3.—Blood thromboplastin generated in a mixture with platelet factor and $\text{Al}(\text{OH})_3$ -treated plasma by: (1) normal serum; (2) neodymium serum 90% + a mixture (equal parts) of P.I.D. and Christmas serum 10%; (3) neodymium serum 90% + normal serum 10%; (4) neodymium serum 90% + Christmas serum 10%; (5) neodymium serum 90% + P.I.D. serum 10%; (6) neodymium serum alone.

The addition of normal serum to neodymium serum was more effective in correcting thromboplastin generation than the addition in the same concentration of either phenindione or Christmas serum separately. The addition of mixtures of phenindione and Christmas sera (equal parts) to neodymium serum resulted in as good a correction of blood thromboplastin generation as the addition of normal serum in the same concentration (Fig. 3). These findings indicate the presence in the neodymium serum of an inhibitor, weakened by dilution, both of Christmas factor and of factor X. It was found, moreover, that neodymium added to normal serum *in vitro* had this inhibiting effect, so that it does not need to be present during clotting to produce its action on those serum factors.

Recent studies of Bergsagel (1955) indicate that calcium interacts with Christmas factor at an early stage in the

With regard to the results of tests on oxalated plasma, the findings of Thies (1954) are important, and we have confirmed them. He found that, on standing, the Quick test clotting-time of oxalated plasma from neodymium-treated subjects shortened considerably, owing to the formation of neodymium oxalate and hence the liberation of "prothrombin" to take part in the reaction. Our one-stage tests were

formation of blood thromboplastin, and it is possible that neodymium displaces calcium from combination with one or more of the proteins involved in this reaction. In their chemical properties calcium and neodymium are similar enough to support such a possibility and dissimilar enough to be biochemically non-interchangeable. Neodymium may in fact be an antimetabolite of calcium in the blood coagulation process, although we have found that excess of calcium does not prevent the action of neodymium *in vitro*. A more probable explanation of the actions described is selective combination with plasma proteins, as described by the German workers.

Summary

In intravenous doses of the order of 5 mg. per kg. in man and rabbits, neodymium 3-sulpho-isonicotinate leads to impairment of intrinsic blood thromboplastin generation by inhibiting two factors normally present in serum—Christmas factor and factor X—and also to variable reduction in factor VII (stable factor, S.P.C.A.) activity. There is no detectable effect on prothrombin. The effect is demonstrable in four hours and lasts for 24 hours. With much larger doses in animals, in addition to the above effects the clotting-time of whole blood is prolonged and the activity of antihæmophilic globulin is reduced.

[Clinical trials since this paper was written in April, 1956, have revealed the presence of hæmoglobinaemia in some patients receiving the drug. Further studies of the toxicity of neodymium in animals and man are in progress.]

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FARMER'S LUNG IN RADNOR AND NORTH BRECONSHIRE A REPORT OF TEN CASES

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An acute or subacute respiratory illness of farm workers developing after exposure to mouldy hay and known as farmer's lung was first reported by Campbell in Cumberland in 1932. Fawcitt in 1936 and 1938 described further cases occurring in Westmorland and Cumberland. Törnell (1946) reported eight similar cases from Sweden under the term "thresher's lung," and Sweeney (1952) four cases occurring in North-West Ireland. In 1953 Fuller had collected 32 cases in Devon since the end of the last war and published a review of the subject. Although the condition has been fully described, a report of a further ten cases is considered to be of sufficient interest to justify publication, it being

felt that not enough attention has been drawn to this occupational hazard of farm workers, and the condition may be more prevalent than it was previously thought to be.

Incidence

All but the first case in the present series were seen within a period of four months, some of them within the same week and two actually on the same day (see Table I). The epidemic occurred mainly in the early part of the year when stored hay is old and dusty and liable to have developed moulds if incompletely dried before harvesting. All the patients developed the disease after exposure to dust-laden air in cow-houses and hay-barns during hand-feeding of cattle. The complaint that the hay was particularly "mouldy" on account of the poor harvest weather in 1954 was unanimous, and most of the victims considered this to be the cause of their symptoms. All the patients lived in the hilly district of mid-Wales, where rainfall and humidity are high, and it is worth recalling that cases previously described in the British Isles also occurred in hill areas. In the present epidemic no other victims were discovered where contact to mouldy hay was known to exist. The fact that out of a total of 17 workers exposed at six farms only six were affected suggests that other factors than mere inhalation of hay dust must be involved. Age did not seem to play a part, as this ranged from 29 to 73 years. No females were included in the series, but the case of a female farm worker seen in a previous year is described later.

Clinical Features

Marked dyspnoea on exertion developing soon after contact with mouldy hay was the prominent feature in all cases. This was usually present for several weeks and was the main reason for referring the patients to the chest clinic. Slight cough with or without expectoration was usual. Occasionally there was loss of appetite with some loss of weight. Physical signs were often absent, but when present consisted of fine basal crepitations. The chest radiograph in all but one case showed fine mottling confined mainly to the middle and lower zones, corresponding with the appearances seen in the cases classified by Fuller as Phase 2. The exception was Case 8, in which no pulmonary changes were present (Phase 1), but the diagnosis was based on the similarity of the history to that of other cases in the area and the patient's response to treatment.

The main features of each case are summarized in Table I.

Progress and Treatment

Response to treatment had been poor in every case until the real nature of the condition was recognized and potassium iodide administered in large doses, when improvement followed. In fact this response to potassium iodide tended to confirm the diagnosis. Avoidance of further contact with hay dust was also insisted upon, and in most cases symptoms ceased within a month. X-ray changes, however, took at least three months to clear up. All patients were back at work within one to three months of their first attendance at the clinic. One patient (Case 4) appeared to go downhill so rapidly with dyspnoea, cyanosis, and loss of weight that his removal to hospital became necessary before improvement in his condition occurred. Antibiotics were not given except in one case (No. 6), which was complicated by a secondary bacillary infection of the respiratory tract. The patient was given a course of penicillin, which cleared a localized area of pneumonitis as shown by the radiograph.

Differential Diagnosis

In an outbreak such as that described here the typical history of severe dyspnoea following contact with mouldy hay or corn coupled with characteristic radiological appearances makes the diagnosis comparatively easy. Diagnosis may be much more difficult, however, in sporadic cases, as is illustrated by the following three cases seen in previous years.

(a) A farm worker aged 21 complained of retrosternal pain on walking which had been present for six weeks when he was seen