of the latter being to prevent such growth. That it has this effect there can be no question, as many studies have shown, one of them, by B. J. Smits and his colleagues in the B.M.J. 

However, in patients in this trial who were given tetracycline without nystatin the proliferation of Candida had no observable clinical effects. The evidence in this and other trials connecting such proliferation with symptoms is either non-existent or conflicting, as is the evidence that the addition of nystatin prevents symptoms of disturbance in the alimentary tract.

Previous studies of this kind are reviewed and some are adversely criticized in the report of a further trial organized by the British Tuberculosis Association and published at page 411 of the B.M.J. this week. It was conducted at eight centres on a double-blind basis, patients being randomly allocated to two groups, receiving either 2 g. tetracycline alone daily for 10 days, or this dose together with the usual dose of nystatin. All the mycological studies were carried out in one laboratory, at the Westminster Medical School. It is claimed that the procedure for eliciting symptoms was free from fallacies entailed in methods of inquiry used in some previous trials. Many of the patients were elderly chronic bronchitics; some were having antibiotic treatment at the time of admission, and some already had gastrointestinal symptoms. The total number of such symptoms diminished slightly during the 10 days' inpatient treatment, but there was no significant difference in their frequency in the two groups. Indeed, such differences as there were, particularly in the frequency of "flatulence" or of "softer or liquid stools," appear to favour treatment with tetracycline alone. There was the usual wide and highly significant difference in the percentage of rectal swabs positive for Candida at the end of the treatment period, but this finding was unrelated to symptoms. In the group given only tetracycline the percentages with and without symptoms from whom Candida was isolated were 37 and 38%. The authors have thus failed to "show any association between candida and gastrointestinal symptoms normally attributed to chemotherapy," and conclude that "the addition of nystatin to tetracycline cannot be justified" as a measure for preventing such symptoms.

If this conclusion is accepted it will clear the air, and the routine administration of this combination, to which there are other objections, will appear to be usually undesirable. This is not to say that combined treatment is never indicated. A fortunately very small minority of patients treated with tetracyclines develop overt candidiasis which may involve the throat and bronchi, the oesophagus or the bowel, operation sites, and even the blood stream. These patients are usually severely debilitated by the primary disease or by some other underlying condition. Since the source of the infection is almost certainly the alimentary tract, protection with nystatin by mouth is indicated whenever it seems possible that this complication can arise.

The problem of preventing gastrointestinal disturbances caused by tetracyclines remains. For any of those attributable to a direct action of the antibiotic on the gastric or intestinal mucosa it appears insoluble, unless perhaps by using newer but less well-tried tetracycline compounds, of which one at least forms a nearly neutral solution and several are said to be better absorbed. If changes in the intestinal flora are responsible for diarrhoea, these perhaps deserve further study. Another approach is bacterial replacement therapy. There is evidence that antibiotic-resistant Lactobacillus acidophilus can be implanted in the bowel during broad-spectrum antibiotic treatment with beneficial results. This treatment has also been shown to suppress the growth of staphylococci in the bowel during treatment with tetracycline.

The place of this kind of treatment is still uncertain, and some of the claims which have been made for it in other connexions will not bear critical examination, but its use in the type of case discussed here appears to be logical and to deserve further study.

Heavy Chain Disease

Seven cases have now been described of an unusual form of lymphoma in which the malignant cells make an excess of the Fc fragment of the "heavy" chains in the immunoglobulin G molecule. This paraprotein, or "M" component, is found in the serum of the patient. On paper electrophoresis it gives rise to a narrow spike or an obliteration of the trough between the β and γ globulin peaks. It also appears in the urine. Unlike the Bence Jones proteins excreted in the urine in multiple myeloma, which immunologically represent the "light" chains common to all classes of immunoglobulin, the Fc fragments in heavy chain disease do not precipitate and then redissolve on progressive heating of the urine. On electrophoresis of concentrates of urinary protein they can be shown to have the same mobility as the abnormal Fc protein found in the serum, and this is of great diagnostic significance in differentiating the new disease from multiple myeloma with reactive proteinuria.

Heavy chain disease appears to give rise to a fairly distinct clinical picture. Six of the seven patients have been middle-aged men who presented either with painful, tender, enlarged lymph nodes or with loss of weight and weakness. About half the cases ran a rapid course, with death in a few months, while in others there was temporary spontaneous regression of the lymphadenopathy and survival for several years. A special clinical feature noted in four of the cases was oedema and redness of the uvula and soft palate. None of the patients had any bone pain or the x-ray changes seen in multiple myeloma.

The proteinuria varied from 50 mg. to 15 g. per 24 hours in different patients and tended to increase in those who survived for several years. As in myeloma and in Waldenström's macroglobulinaemia, the amount of the abnormal γ-globulin in the serum also increased as the disease progressed, and in most cases this increase was accompanied by a reduction in the synthesis of normal IgG, with the result that the patients nearly all died of infections, especially pneumonia.

owing to deficiency of antibodies. The only female patient described so far presented with a severe normochromic anaemia with hepatosplenomegaly, and the lymph-node enlargement could be detected only in mediastinal glands on x-ray examination. Two of the patients had occult prostatic cancers in addition to the malignant lymphomas.

Histologically, heavy chain disease is characterized by proliferation of reticulum cells mixed with abnormal lymphoid and immature plasma cells. In two cases the diagnosis of Hodgkin's disease was entertained at first owing to the presence of binucleate cells resembling the Reed-Sternberg cell.

The nature of the abnormal protein has been thoroughly studied. The IgG molecule consists of two "heavy" polypeptide chains and two "light" chains; they are linked together by disulphide bonds. The heavy chains can be split in half at a certain point by papain. This separates the Fc (=crystallizable) fragment, which consists of the rear portion of the heavy chain pair from the front half of the heavy chains, called Fd fragments, which remain attached to the light chains to form the Fab (=antigen-binding) portion of the molecule.

The paraprotein made in heavy chain disease is almost identical with the papain-split Fc fragment of normal IgG. There may be slight variations in the length of the chains in different patients, but the most interesting results have come from a study of the amino-acid sequences of the "N-terminal" end of the chains, where synthesis of the molecule begins, and of the "C-terminal" end, which represents the last portion synthesized. Experiments have shown that the heavy chain is made in one sequence instead of the Fd and the Fc halves being made separately and then joined up. Therefore it is of great interest that in heavy chain disease the N-terminal and C-terminal ends are both normal, while the light chains and the intervening part of the Fd fragments are missing. This suggests that in the clone of malignant cells a deletion has occurred in the genetic mechanism which directs the production of this part of the heavy chain.

The serum proteins found in patients with myeloma have been invaluable for charting the various classes and subclasses of immunoglobulin. The Fc fragments carry the antigenic determinants for the four known subclasses of IgG. And, since the distribution of different myeloma globulins in the population follows the pattern found in normal individuals, it is likely that observations on further cases of heavy chain disease will disclose the existence of Fc fragments corresponding to other immunoglobulin classes.

Control of Measles

Sunday, 23 January 1966 was called "End Measles Sunday" in Rhode Island, U.S.A., because a large-scale operation in preventive medicine was undertaken then. Its purpose was to raise the proportion of the juvenile population that was resistant to measles to such a level that epidemics of the disease would no longer be possible—in other words to bestow on it "herd immunity." A recent report indicates that this goal has been successfully achieved. For this reason, and because Rhode Island is one of the only two States in the U.S.A. which is comparable in both area and population to a British county, the experiment is of interest here in Britain, where large-scale vaccination against measles is now being undertaken.

The strategy, tactics, and execution of the initial immunization campaign are reminiscent of those of the diabetes detection drive undertaken in Bedford in April 1962. Both entailed closely co-ordinated planning between local health authorities, the doctors responsible for the clinical care of the population, and the staff of a medical school (in one case Guy's Hospital and in the other Yale University). Both were preceded by a carefully planned publicity campaign; both involved the massive and enthusiastic assistance of voluntary workers; both reached between 65 and 70% of the target population; and both were followed by intensive surveillance.

In Rhode Island a vaccine made from a live attenuated virus (Schwarz) was administered with multiple-dose jet injector guns. Surveillance was the responsibility of an epidemic intelligence officer posted to Rhode Island from the National Communicable Disease Centre, Atlanta, Georgia. Every new case of measles was reported to the State Department of Health, and when possible the cases were examined clinically by members of the staff of that department. In all, the study lasted 15 months, for the first six months of which the serum of all suspects was subjected to serological investigation.

Of 71 suspected cases, 42 (59%) were found to be clinically compatible with measles. Blood was obtained from 32 of these but in only 10 (31%) could serological confirmation of the diagnosis be found. A further 17 had antibody patterns suggestive of measles infection in the past.

Of the 42 "clinically compatible" cases 14 were solitary, indicating a high prevalence of immunity among their contacts, and the remaining 28 occurred in five clusters, four of which comprised fewer than six persons and the fifth comprised 14. The most frequent source of the disease was an out-of-State visitor; the families of men in the Forces were often affected. The incidence of the disease per 100,000 during the 15-month period was 5.0 among the highest of three social classes, 6.4 in the middle, and 3.0 among the lowest. It is assumed that this distribution is because the poorest people were the least likely to have out-of-State visitors.

From the clinical point of view many of the cases were bizarre. Fourteen of the 42 developed in people who had had previous disease, and in one of these there was serological evidence in support of the view that a second attack did indeed occur. In contrast several patients had an illness in every way typical of measles—including Koplik's spots in three of them—without any serological evidence of having recently been infected by the measles virus.

The Rhode Island experiment has some valuable lessons for us. To begin with it shows clearly that a well-planned and executed single-day campaign can transform a susceptible population to one which has "herd immunity." Secondly it shows that artificially endowed herd immunity to measles is every bit as effective as the theorists would lead us to expect and that the side reactions are not sufficiently serious or frequent to interfere significantly with school attendance. In