we allow mothers to be infected. For all these reasons we cannot afford to let up in our aseptic and antiseptic precautions.

And we should perhaps remember that large parts of the world have not yet achieved the high standard of obstetric practice that now obtains in the most progressive countries. In those less fortunate countries unskilled midwifery will still take its heavy toll.

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IMMEDIATE AND REMOTE RESULTS OF CHLOROETHYLAMINE TREATMENT OF HODGKIN'S DISEASE

BY

L. F. LARIONOV, M.D.

Director of a Department, Institute of Experimental Pathology and Therapeutics of Cancer, Academy of Medical Sciences of the U.S.S.R., Moscow

The use of chloroethylamines in the treatment of Hodgkin's disease was proposed by a group of American workers in 1946 (Gilman and Philips : Goodman *et al.*). It was pointed out that chloroethylamines were chiefly used for the palliative treatment of generalized advanced cases of Hodgkin's disease and for cases resistant to *x*-ray therapy. It was emphasized that localized earlier stages of the disease should continue to be treated with *x* rays. This opinion was essentially supported by other authors, although some investigators, particularly British (Wilkinson *et al.*, 1953), gave a higher evaluation of the treatment with chloroethylamines, especially tri-(2-chloroethyl)amine.

The therapeutic activity and clinical use of chloroethylamines have been studied by us since 1947. As regards the method of application of these compounds, the indications for their use, and their value in treatment we disagree to some extent with the American authors. While we started treatment with di-(2-chloroethyl)-methylamine hydrochloride ("embichin"), we began using another chemical compound from 1950 onwards. It is the object of this paper to present our findings, paying special attention to the remote results of treatment of Hodgkin's disease with chloroethylamines, no account of which has apparently been published.

General Dosage Scheme

The intravenous injection of chloroethylamines in a daily dose of 0.1 mg. per kg. body weight for four days (maximum six days) is the most widely used method of therapy. Some authors recommend two injections of a double dose (Ap Thomas and Cullumbine). Even after such a short course of treatment the maximum therapeutic effect as well as depressive side-effect upon haemopoiesis becomes evident, therefore treatment cannot be properly individualized.

Experimental studies on rabbits carried out by my assistant G. L. Zhdanov showed that the depressive effect of embichin upon haemopoiesis depended to a high degree upon the intervals between injections. Prolongation of the intervals up to 48 hours, and particularly up to 78 hours, when haemopoiesis in the bone marrow has had time to recover to some extent, considerably reduces the action of embichin upon the blood-forming organs. For this reason, and on the basis of the statement above concerning individualization of treatment, we injected the drug three times a week—that is, with 48- and 72-hour intervals. With such intervals it became possible, and even necessary, to make not four to six but eight to twenty injections. The therapeutic effect can be noted during treatment, and this makes it possible to control the latter. In addition full advantage is taken of variations in sensitivity of granuloma to chloroethylamine drugs on the one hand, and in the bone marrow on the other, especially their ability to regenerate, which is greater in the bone marrow than in granulomatous tissue.

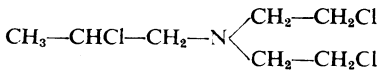
Experience has shown that the desired therapeutic effect —that is, complete regression of all involved nodes—can be obtained only by simultaneous and marked depression of haemopoiesis, the leucocyte count being reduced to 2,000–3,000 per c.mm. It is our experience, however, that this level of depression of the bone marrow is not dangerous and haemopoiesis is recovered within three to four weeks. Accordingly we continue injections until the leucocyte count falls to 2,500–3,000 per c.mm. Sometimes a few days after the last injection the leucocyte count falls to 1,500–2,000 per c.mm. The number of injections needed to cause this leucopenia in different patients varies according to the condition and reaction of the blood system, on the stage and type of the disease, and whether *x*-ray therapy, which increases the sensitivity of the haemopoietic system to chloroethylamines, has been given previously. We usually succeed in making from eight to sixteen injections. If one course of injections is insufficient to cause complete regression of the nodules, a further course is given six to eight weeks after the first one. In this way we are able to obtain the maximum therapeutic effect.

No other special measures to stimulate haemopoiesis other than transfusion of 100 ml. of blood once or twice a week are adopted. According to our findings such drugs as nucleic acid salt of sodium or pentoxyl will stimulate the essential pathological process to a greater degree than normal haemopoiesis.

Search for a New Drug

Di-(2-chloroethyl)methylamines are known to cause vomiting and nausea in a large proportion of cases. A special study of this phenomenon by our co-worker E. I. Khomchenovsky showed that vomiting was caused by a reflex from the small intestine which was transmitted to the vomiting centre through the vagus nerve. The failure of our efforts to overcome this side-reaction of embichin led us to seek another compound having a less marked effect. We also wished to find drugs with a more pronounced effect upon the lymphatic system and a weaker action on the bone marrow.

The systematic search for more suitable compounds among homologues and analogues of embichin was carried out by us in collaboration with V. G. Nemetz, professor of chemistry at the Laboratory of Experimental Therapeutics of Cancer of the Institute of Oncology, Academy of Medical Sciences, Leningrad, in 1947–50. At first the compounds in which two valences of nitrogen were occupied by two 2-chloroethyl groups and the third by the ethyl, *iso*-propyl, butyl, and 2-chloropropyl groups were synthesized and studied on animals. The compound with one methyl, one chloroethyl, and one 2-chloropropyl group and the compound with two chloropropyl groups were also studied. As a result of this investigation our co-worker S. A. Papojan, in experiments on rabbits, found that one of the synthesized compounds—namely, 2-chloropropyl-di-(2-chloroethyl)amine hydrochloride:



has a stronger effect upon lymphopoiesis than embichin and a milder effect on the bone marrow. An increase in the number of pseudo-eosinophils in the blood and a decrease in that of lymphocytes were observed after a few injections of small doses.

This compound was tried in the clinic of the Institute of Oncology in 1950–1. Its more pronounced activity upon lymphopoiesis and milder effect upon bone marrow were confirmed. Fortunately, it proved that this drug, particularly in Ringer's solution, had a less marked side-effect on the gastro-intestinal tract.

This new drug, called "novoembichin," has been widely used since 1952 in the medical institutions of the U.S.S.R. and has now replaced di-(2-chloroethyl)methylamine. During the last four years we have used only novoembichin in the treatment of Hodgkin's disease. It is given in larger doses than embichin, usually 9 mg. (less often 8 or 10 mg.) for adults. The number of injections varies from eight to sixteen. For the treatment of lymphoid leukaemia we use a dose of 8 mg., and for myelogenous leukaemia 10 mg.

Below are described the immediate and remote results of treatment of Hodgkin's disease with embichin and novoembichin according to our method. From 1949 to 1955 I have participated in the treatment of about 300 patients, 100 of them at the Institute of Oncology at Leningrad (1949–51) and about 200 at the Institute of Experimental Pathology and Therapeutics of Cancer and other institutions in Moscow (1952–5).

Stages of Hodgkin's Disease

In such a severe disease as lymphogranulomatosis, which tends to be generalized and to relapse, the results of treatment necessarily depend to a large extent upon the stage of the disease at which it is instituted and upon the type of disease, whether it is of slow or rapid course. Consequently, in order to summarize the results and to make a comparison with *x*-ray therapy it was first of all necessary to note the stages of the disease.

We proposed to distinguish between four clinical stages in the course of Hodgkin's disease by analogy with malignant tumours, which are divided into stages in the U.S.S.R.

In the first stage are those patients with the initial form of the disease, in which the pathological changes are confined to one group of lymph nodes (for instance, in the cervical region) and general clinical symptoms are absent. The disease does not progress for some time in most cases at this stage, apparently owing to the effectiveness of the bodily resistance. This stage, closely resembling the latent period described by other authors, lasts several months, sometimes one or two years, but is seldom diagnosed as Hodgkin's disease at this period.

The second stage is also the initial period of the disease, but the process is beginning to develop, indicating a failure of the compensatory forces of the body. There are still mild general symptoms, with a rise in evening temperature. Granulomatous changes in the lymph nodes and involvement of other nodes, such as in the mediastinum or axillary region, take place, but the nodes are still not greatly enlarged. This stage can be designated the initial progressing stage.

The third stage (the stage of significant spread along the lymphatic system) characterizes the completely developed illness with marked general symptoms, loss of working capacity, fever, and pruritus. The changes in the lymph nodes have progressed and involved many groups of nodes, some of which become much enlarged.

The fourth stage includes patients with anaemia, emaciation, loss of working capacity, generalized pathological changes in the lymph nodes, and sometimes pulmonary, pleural, and bony involvement. At this stage bodily resistance becomes almost exhausted.

The above classification is applied to chronic cases of Hodgkin's disease, as it is almost impossible to differentiate these stages in acute cases and in those running a rapid course. It is difficult to define the early stages in those forms of the disease in which the mesenteric nodes are initially affected. It is advisable to classify patients with chronic Hodgkin's disease according to whether the course is slow, moderate, or rapid.

Of the 300 patients admitted for treatment, about 25% were classified as in the second stage, about 50% in the third stage, and about 25% in the fourth stage.

Immediate Results of Treatment

The data presented below concern the immediate effect of the treatment of Hodgkin's disease with embichin and are based on observations made on the whole series.

This treatment gave immediate positive results in nearly all the patients. These included a decrease in size of the affected nodes or their complete regression, disappearance or amelioration of general symptoms, such as fever and pruritus, and partial or complete recovery of working capacity. The best results were observed in patients in the second or the beginning of the third stage, with affected cervical, mediastinal, and axillary nodes, who had received no previous treatment or only one or two courses of radiotherapy. The worst results were observed in patients at the end of the third and fourth stages, particularly those with involvement of the retroperitoneal nodes, and in a number of patients previously subjected to radiotherapy repeatedly applied to various sites. Occasionally in such patients chemotherapy had to be discontinued because of the rapid depression of haemopoiesis.

In spite of good immediate results, relapses were observed in many cases. However, in four patients out of 25 whose treatment was started in the second stage (none of whom had been treated previously) no relapses have occurred to date; one was followed up for three years, one for four years, and the third for six years after the first course of treatment, and one patient for four years after the second course. Other patients had relapses in six months to a year after each course of treatment.

In patients in the third and fourth stages, particularly those with affected retroperitoneal nodes and who had received radiotherapy, relapses occurred earlier, in from two to six months, seldom later. To prevent or delay relapses it proved helpful in a few cases to give an additional (prophylactic) course of injections of shorter duration soon after the main course of treatment. In many cases further courses of treatment during relapses gave the same good results as the first course. It is most important to repeat the treatment at the onset of the relapse when symptoms first appear. If treatment is delayed, not only do relapses occur but the next stage of the illness sets in, with deterioration in the patient's condition. Even short delays should be avoided, for relapses often tend to progress rapidly. To each of the patients in the present series from one to six repeated courses of injections of embichin and novoembichin were given. In some cases repeated courses of injections became difficult owing to the poor condition of the veins, so that radiotherapy was sometimes necessary.

Late Results of Treatment

The remote results are based on only one group of patients whose treatment was started between 1949 and 1951 at the Institute of Oncology at Leningrad—that is, from four to six years ago. To evaluate the results of chemotherapy 60 patients were selected out of 100 in whom this was the essential method of treatment. Treatment was begun with embichin and continued in this way in 36 cases. The other 24 patients had originally been treated with *x* rays (one or two courses), and received chemotherapy later. In this group are included a few patients treated chiefly with embichin but receiving *x*-ray therapy as an auxiliary method of treatment. Out of the 60 patients, treatment of 25 began in the second, of 23 in the third, and of 12 in the fourth stage. Treatment of these patients was at first carried out at the clinic of the Institute of Oncology by the assistants E. M. Koozmina, O. N. Nikonova, and E. A. Tzel, and since 1951 by M. A. Zeev, under my guidance.

The late results of treatment are presented in Table I, in which, owing to the small numbers, the third and fourth stages are grouped together.

It can be seen from the Table that 20 patients (80%) out of 25 to whom embichin was administered in the second stage of the disease lived to the end of the third year, and 7 patients out of 15 in whom treatment was begun in 1949 and the early months of 1950 remained alive to the end of the fifth year. Only one-third of the patients in whom treatment was begun in the third and fourth stages were alive by the end of the third year, and one patient out of 15 was alive at the end of the fifth year. Consequently the indices for these stages are much worse than for others. The interval from the onset of illness till the beginning of treatment in patients in the second stage varied from three months to one and a half years, with an average of about one year. We still cannot calculate the average expectation of life after the onset of symptoms for patients of this group, as 50% of them are still alive.

TABLE I.—*Late Results of Treatment with Embichin of 60 Patients with Hodgkin's Disease: Treatment Started in* 1949–51

Stage	No. of Patients	Patients Alive since the Beginning of Treatment		
		1 Year	3 Years	5 Years
II ..	25	25 (100%)	20 (80%)	7 (47%) out of 15
III and IV ..	35	28 (80%)	13 (37%)	1 (7%) out of 15
Total ..	60	53	33	8

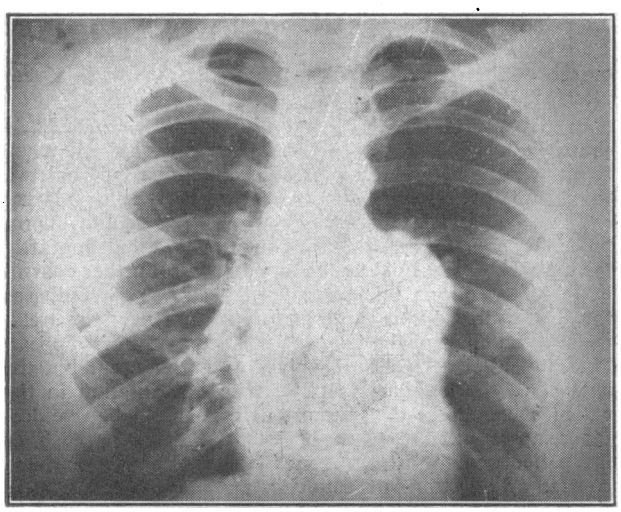


FIG. 1.—Case 1: Radiograph before treatment, showing enlarged left mediastinal lymph nodes.

Illustrative Cases

Below are brief details of three patients whose treatment was started in 1949 and the beginning of 1950, and who at present remain clinically healthy.

Case 1.—A male engineer aged 27 was first seen in May, 1949. Examination revealed enlarged lymph nodes in the left supraclavicular region and the mediastinum (Fig. 1). Biopsy of a supraclavicular node confirmed the diagnosis of Hodgkin's disease. After 19 injections of embichin (given in the out-patient clinic) the leucocyte count fell to 1,000 per c.mm. within a few days, and all nodes disappeared (Fig. 2). The blood picture returned to normal after six weeks. No other treatment was given. There has been no relapse for six years, and he has full working capacity.

Case 2.—A female worker aged 32 fell ill in March, 1948, and was first seen by us in 1949. Examination showed enlarged left supraclavicular and mediastinal lymph nodes (Fig. 3). Biopsy confirmed a diagnosis of Hodgkin's disease. After treatment in March, 1949, all nodes disappeared (Fig. 4). In May a prophylactic course was given, and this was followed by remission for two years and three months. During relapse in June, 1951, a second course of ten injections was given. No relapse for four years. Now, six and a half years after treatment was started, she has full working capacity.

Case 3.—A female student of a technical school, aged 18, fell ill in January, 1949. Hodgkin's disease was diagnosed in March, 1949. *X*-ray therapy was applied to the right supraclavicular nodes. Relapse occurred in ten months, the same area being affected. In February, 1950, the first course of treatment with embichin was given. Relapse occurred in 1952 and 1954, when two further courses of injections were given in the policlinic. Now, five years and eight months since the beginning of treatment, she is free from symptoms. She has graduated from the technical school and has been working all this time. At present there are no signs of the disease. Last year she married.

Chemotherapy and Irradiation Compared

The above case reports show that adequate treatment of patients in the early stages of Hodgkin's disease with chloroethylamines gives satisfactory results. Therefore we cannot agree with those authors who consider such treatment to be suitable only for patients with generalized disease and resistant to radiotherapy. Nor do we agree with the statement that patients in the early stages, particularly when the process is localized, should receive only *x*-ray therapy. On the contrary, we believe that in the early stages of Hodgkin's disease chemotherapy is at least optional; moreover, that in many cases treatment of the early stages, particularly with cervical and mediastinal localization, must begin with chemotherapy, which exerts a better therapeutic

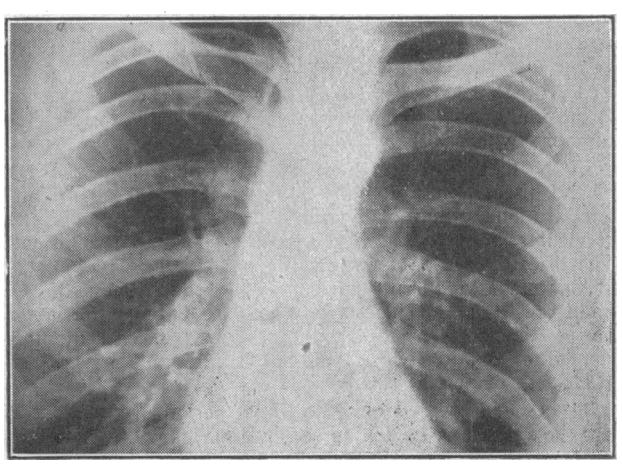


FIG. 2.—Case 1: *X*-ray appearances after treatment.

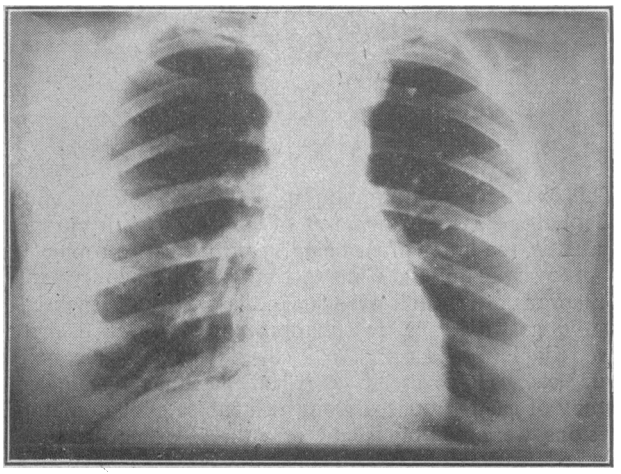


FIG. 3.—Case 2: Radiograph before treatment, showing enlarged left mediastinal lymph nodes.

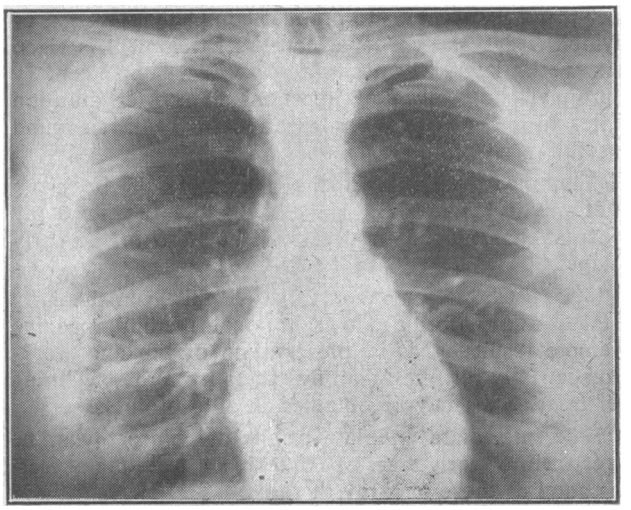


FIG. 4.—Case 2: *X*-ray appearances after first course of treatment (March, 1949).

effect upon the body as a whole than localized radiotherapy and inhibits the process in nodes not clinically evident, wherever they are situated.

In fact, review of data concerning the late results generally obtained in the treatment of Hodgkin's disease with *x* rays shows that the late results obtained by us with chemotherapy are equally as good. This emerges clearly, for instance, from the findings of Videbæk (1950) and of Devois and Decker (1953), and also from comparison with the results of radiotherapy of 232 patients with Hodgkin's disease obtained at the Institute of Oncology at Leningrad during 20 years (1928–49) and recently summarized by R. L. Boner (1955) (Table II).

TABLE II.—*Late Results of X-ray Therapy and Chemotherapy of Hodgkin's Disease*

	Author	Patients Surviving after Beginning of Treatment	
		3 Years	5 Years
Radiotherapy	Videbæk	50%	25%
	Devois and Decker	40%	21%
	Boner	40%	16%
Chemotherapy	Our findings (all stages together)	58%	33%

According to our information, similar results of the chemotherapy of Hodgkin's disease have been obtained in the Institutes of Roentgenology, Radiology, and Oncology at Kiev (T. S. Yankovskaya) and at Voronezh (Z. V. Shamina).

Combined Methods of Treatment

We do not wish to belittle the importance of radiotherapy in the treatment of Hodgkin's disease. Moreover, we believe that the rational combination of chemotherapy with radiotherapy is the best method of treating this disease, just as the combination of surgery and irradiation is employed in the treatment of a number of malignant tumours. Each of these methods has its own advantages and disadvantages.

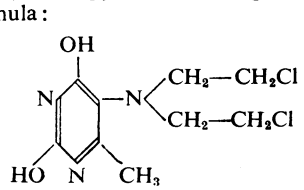
The main form of combination we use consists of an initial course of embichin and then, if the lymph nodes have not completely regressed, irradiation of the nodes which remain enlarged in place of an additional course of chemotherapy. Usually irradiation of one or two sites is required. In this way the effect of the chemotherapy is supplemented and secured. On the other hand, comparatively small total doses of *x* rays leaves open the possibility of applying chemotherapy again without the risk of weakening the functional capacity of the haemopoietic system which is often observed with chemotherapy after repeated and intensive irradiation of many fields.

Another way of combining chemotherapy with radiotherapy is to use both methods alternately in subsequent relapses. This method delays the development of resistance to *x* rays and makes it possible to treat cases with poor tolerance to chloroethylamines, those in which the blood-forming organs are sensitive to these drugs, and those with a poor venous system.

We have repeatedly tried both these forms of combined treatment with success. The least successful method, in our opinion, is the use of *x*-ray treatment alone from the onset of the illness and in subsequent relapses, with the addition of chemotherapy only when the disease has become advanced. When used in this way, as recommended by a number of investigators, chemotherapy does not give as good results as may be obtained in the early stages of the disease, although it often leads to remission.

A New Chloroethylamine

Recently we have discovered a new drug belonging to the group of chloroethylamines which has the advantage that it can be given by mouth. This is 2:6-dioxy-4-methyl-5-(2-chloroethyl) aminopyrimidine ("dopan"), which has the following formula:



This has been synthesized according to my suggestion by V. G. Nemetz and studied on animals by my assistant G. N. Platonova, whose experiments showed that the drug was almost free from side-effects upon the gastro-intestinal tract. In clinical trials at the Institute of Experimental Pathology and Therapeutics of Cancer under the direction of Professor N. N. Blokhin the dose for adults was found to be 8–10 mg., which can be administered twice weekly. Judging from the immediate results this drug is as effective as embichin in Hodgkin's disease.

Summary and Conclusions

Among the aliphatic chloroethylamines, 2-chloropropyl-di-(2-chloroethyl)amine hydrochloride (novoembichin), with a milder side-effect upon the gastro-intestinal tract and a weaker action on the bone marrow than other compounds of the series, is the most suitable drug for the treatment of Hodgkin's disease.

The prolonged method of treatment with thrice-weekly injections has been found the most suitable. Usually 8 to 16 injections are necessary. Injections are continued until the leucocyte count falls to 2,500–3,000

per c.mm. If this fails to produce complete regression of lymph nodes an additional course of treatment is given six weeks later. To prevent relapses a supplementary (prophylactic) course of injections of shorter duration after an interval of two to three months has been found useful.

Treatment with chloroethylamines should be given not only in the advanced stage of the disease when *x*-ray therapy has proved unsuccessful, but also in the early stages.

With such treatment, provided it is given in the early stages and according to a rational method, positive remote results—that is, preservation of life and working capacity for more than five years from the beginning of treatment—may be obtained in 50% of cases.

The immediate and late results of chloroethylamine treatment of early cases of Hodgkin's disease are at least as good as those of *x*-ray therapy.

The above two treatments are applicable in combination, the following two methods having been found useful in our hands: (1) an initial course of chemotherapy is given, and this is followed after an interval of six to eight weeks by *x*-irradiation of nodes which have not completely regressed; or (2) the two methods of treatment are applied alternately in subsequent relapses.

A new drug—2:6-dioxy-4-methyl-5-(2-chloroethyl) aminopyrimidine (dopan)—has been developed which, as it can be administered orally and has only a slightly toxic action on the gastro-intestinal tract, renders the chemotherapy of Hodgkin's disease more convenient for the patient, one tablet being given twice weekly for three to five weeks.

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The Minister of Health, Mr. R. H. TURTON, has written to hospitals to ask them to re-examine any remaining restrictions on the daily visiting of children in hospital. His letter is based on advice given by the Standing Medical Advisory Committee and endorsed by the Central Health Services Council on a number of difficulties shown by a review in 1954 to be the main obstacles to the universal acceptance of daily visiting. One of the main problems concerns infectious diseases hospitals. The Minister is advised that subject to certain safeguards frequent visiting can be allowed and, indeed, is already allowed in a number of such hospitals. Safeguards suggested include the presence of sufficient nursing staff to ensure close supervision of the conduct of visiting parents, the wearing of protective clothing by visitors, and the application to them of the routine measures for the prevention of the spread of infection. It is suggested that if visitors are to wear masks and gowns they should, where possible, be put on in the child's sight. Some hospitals which do not allow daily visiting give as the reason the undesirability of admitting visitors on operating days. The Minister is advised, however, that there is no general reason why all visiting on these days should be prohibited.

EFFECTS OF ALCOHOL ON GASTRIC MUCOSA

BY

A. WYNN WILLIAMS, M.D., D.C.P.

Senior Lecturer in Pathology, University of Edinburgh

The excessive consumption of drinks containing ethyl alcohol is generally believed to induce acute or chronic gastritis, the latter often being described as "atrophic"; moreover, many clinicians attribute the dyspeptic manifestations of alcoholism to such inflammation. Theoretically, gastritis is a reasonable expectation, and there is reliable evidence that it does occur in alcoholic subjects. However, in a recent personal histological study of gastric mucosa from such subjects inflammatory lesions were notably slight or entirely absent, even in some inveterate spirit-drinkers. This observation, together with the paucity of histological data referring to the effects of alcohol on the gastric mucosa, suggested the need of a re-evaluation of current opinion. Impressions based only on clinical findings, including gastroscopic and radiological observations, are not always accurate. It is only by the histological examination of fresh gastric mucosa that a true assessment of structual appearances can be made. The problem is clearly of practical importance when it is realized that over £800,000,000 is spent annually in Great Britain and Northern Ireland on alcoholic drinks.

In an attempt to obtain information on the effect of alcohol on the stomach mucosa, a series of biopsy, gastrectomy, and necropsy specimens from alcoholic subjects were examined. In addition, a detailed study was made of the effects of alcohol on the guinea-pig stomach. These investigations and the results obtained are now described.

Human Gastric Mucosa after Alcoholic Excess

An examination was made of gastric mucosa from 25 adults with a history of alcoholic excess. Sixteen of these patients were admitted to hospital for full investigation of vague symptoms apparently related to alcoholism, and gastric biopsy was performed on them, using a modified Australian flexible tube (Coghill and Wynn Williams, 1955). In addition, the portion of stomach from three patients who underwent partial gastrectomy for chronic gastric or duodenal ulcer and six stomach specimens obtained at necropsy were examined; the latter were fixed with formol-saline within one hour of death.

All the tissues were fixed in 10% formol-saline, and paraffin sections were stained routinely with haematoxylin and eosin. Where additional information was required, sections were stained with Southgate's mucicarmine, Motteram's trichrome stain for gastric mucosa, and Masson's trichrome stain.

The pathological changes seen included one or more of the following: loss of glandular elements; "intestinal metaplasia"; replacement of body glands by glands of pyloric type; hyperplasia and nuclear hyperchromatism of epithelium at the mucosal surface; excessive numbers of small round cells, plasma cells, or polymorphonuclear leucocytes in the stroma; oedema; hyperaemia; haemorrhage; fibrosis; erosion; ulceration. The commonest of these were chronic inflammatory changes without specific characters and often mild in degree.

Biopsy Specimens

Two specimens of mucosa were removed from the body of the stomach in each of 16 patients. One patient was a