

appreciable incidence of toxic effects? Probably only time will give a definite answer.

The distinction of a pre-symptomatic homozygote from the heterozygote of Wilson's disease—who, though frequently showing some abnormality in copper metabolism, will not develop the disease—requires the fullest investigation, including liver biopsy. About 10% of heterozygotes have a reduced level of caeruloplasmin in the serum, and concentration of copper in the liver may be moderately increased, though levels above 250  $\mu\text{g./g.}$  dry weight are found only in the homozygous state.<sup>2,4</sup> The histochemical staining of liver biopsies for copper is unreliable, as are several other screening tests such as the presence of a low serum uric acid level or aminoaciduria detectable by chromatography of the urine. The relatively simple radioisotope test developed by S. B. Osborn and J. M. Walshe,<sup>7</sup> in which the counting rate over the liver is compared with that over the thigh after the intravenous injection of copper-64 chloride may not separate the presymptomatic homozygote from the heterozygote, and, indeed, the specificity of this test has been questioned recently after low values have been found in other varieties of cirrhosis.<sup>8</sup> Nevertheless, there can be no question that the diagnosis of a case of Wilson's disease must lead to most thorough and careful examination of the patient's brothers and sisters.

## Helicopters and Medical Emergencies

Air ambulance units in Vietnam carried 94,000 casualties<sup>1</sup> by helicopter in 1967. All military casualties in the war are now within 35 minutes' flying time of resuscitation units on the ground. Again, the value of helicopters in the jungle-covered mountains of the Malay Peninsula is evident from the article by Dr. J. M. Bolton at page 818 of the *B.M.J.* this week. He shows how medical services can be brought right into the heart of singularly inaccessible territory.

Conditions in Great Britain pose very different problems, though even here 100 or so sick and injured persons are carried by helicopter each year. Helicopters are provided by the Services on request by medical officers of health, and their tasks fall into two groups. The first is the removal of sick and injured persons from ships at sea or from inaccessible areas such as mountains or remote islands. The second is the conveyance by air of patients for whom the delay or the disturbance of a long journey by road is considered undesirable. Most of the medical helicopter flights in Britain are of this second type and are arranged at leisure rather than as emergencies. Nevertheless, the helicopters can become airborne within a few minutes of being requested. It is remarkable, and also reassuring, that even in Britain weather very rarely interferes with operations of this sort.

From time to time there have been suggestions that helicopters should play a larger part than they do in the conveyance of injured persons, but such suggestions need to be considered realistically. Unlike the casualties of war, the casualties of peace are not predictable in terms of time, place, and number, and at the present time there can be little alternative to a rather sparse network of machines that are themselves readily available but not necessarily close at hand.

Furthermore, in peacetime the purse strings are tightly drawn and the Services charge £50 or £124 an hour according to the machine that is used. Before calling for a helicopter, doctors should weigh carefully the advantages and disadvantages of the different methods of conveyance and consider particularly the possibility that the slower vehicle may arrive first, since it usually covers a much shorter distance. The larger accident centres should be designed to enable helicopters to land, but we should not expect to see many more of them at work carrying patients.

## L.S.D. and Chromosomes

The question whether lysergic acid diethylamide (L.S.D.) damages the chromosomes is still undecided, but because the drug is used in psychiatric medicine and as a hallucinogen for "kicks" it needs thorough study.<sup>1</sup> In general, work on L.S.D. as a chromosome-breaking agent has been of three types—namely, direct in-vivo studies of people who have taken it therapeutically or illicitly, in-vitro studies of lymphocyte cultures treated with L.S.D., and finally in-vivo and in-vitro studies on experimental animals.

The in-vivo studies on patients have generally proved to be inconclusive and sometimes contradictory. M. M. Cohen and his co-workers<sup>2,3</sup> report chromatid aberrations in a series of 18 patients who had taken different doses of L.S.D. for various times and who had also taken other drugs either previously or at the same time as L.S.D. This group of workers also examined the chromosomes of four children of three mothers who had taken L.S.D. during pregnancy, and found a raised frequency of breakage in two children whose mothers had taken a high dosage (300–600  $\mu\text{g.}$  per dose) of the drug during the first three to four months of pregnancy. Low doses later in pregnancy had an insignificant effect. Similar results were obtained by S. Irwin and J. Egozcue<sup>4</sup> in six out of eight patients taking the drug, and these workers also observed a "Ph<sup>1</sup>-like chromosome" in two users of the drug (the "Philadelphia" chromosome is found in some cases of leukaemia). H. Zellweger and colleagues<sup>5</sup> report chromosome breakage in the parents of a congenitally malformed child who had taken the drug during pregnancy and postulate a causal association between the congenital malformation and the drug, but this needs confirmation. This week Dr. J. Nielsen and colleagues report in the *B.M.J.* at page 801 that they found a statistically significant increase of damaged

<sup>1</sup> *Brit. med. J.*, 1967, 4, 124

<sup>2</sup> Cohen, M. M., Marinello, M. J., and Back, N., *Science*, 1967, 155, 1417.

<sup>3</sup> Cohen, M. M., Hirschhorn, K., and Frosch, W. A., *New Engl. J. Med.*, 1967, 277, 1043.

<sup>4</sup> Irwin, S., and Egozcue, J., *Science*, 1967, 157, 313.

<sup>5</sup> Zellweger, H., McDonald, J. S., and Abbo, G., *Lancet*, 1967, 2, 1066.

<sup>6</sup> Sato, H., and Pergament, E., *Lancet*, 1968, 1, 639.

<sup>7</sup> Loughman, W. D., Sargent, T. W., and Israelstam, D. M., *Science*, 1967, 158, 508.

<sup>8</sup> Cohen, M. M., Hirschhorn, K., and Frosch, W. A., *New Engl. J. Med.* 1968, 278, 223.

<sup>9</sup> Jarvik, L. F., and Kato, T., *Lancet*, 1968, 1, 250.

<sup>10</sup> Jagiello, G., and Polani, P. E., unpublished.

<sup>11</sup> Jagiello, G., *Science*, 1967, 157, 453.

<sup>12</sup> Jagiello, G., *Mutation Res.*, in press.

<sup>13</sup> Alexander, G. J., Miles, B. E., Gold, G. M., and Alexander, R. B., *Science*, 1967, 157, 459.

<sup>14</sup> Auerbach, E. R., and Rugowski, J. A., *Science*, 1967, 157, 1325.

<sup>15</sup> Geber, W. F., *Science*, 1967, 158, 265.

<sup>16</sup> Fabro, S., and Sieber, S. M., *Lancet*, 1968, 1, 639.

chromosomes in five patients treated with L.S.D. compared with controls. To add to the confusion in-vivo studies of blood cultures of eight people who had taken L.S.D.<sup>5-7</sup> failed to show any increase of chromosome or chromatid breakage over the levels observed in controls.

Several criticisms may be made of all these investigations. The first is that the actual dose of the drug L.S.D. taken is sometimes in doubt or is derived from statements made by the users. The second is that other drugs were sometimes being taken at the same time. Cohen and colleagues<sup>8</sup> have tried to investigate some of these drugs, and they report no chromosome breakage. Indeed examination of some of the data published suggests there was a considerable overlap between the findings in the controls and in the persons who had taken the L.S.D. A high level of chromosome breakage appears to be commonly found in some lymphocyte cultures. In-vitro studies of L.S.D. added to lymphocyte cultures<sup>2, 3, 9</sup> have shown that it does produce chromatid aberrations at a fairly low level, but by this technique so do various other commonly used drugs such as acetylsalicylic acid (aspirin) and ergometrine maleate, and the level of breakage is by no means as high as that produced by the antitumour drug streptonigrin.<sup>9</sup>

Two other lines of work are of importance. G. Jagiello and P. E. Polani<sup>10</sup> have shown that L.S.D. has a negligible effect on both male and female meiosis in mice, particularly when compared with substances such as streptonigrin<sup>11</sup> and the antitumour substance phleomycin,<sup>12</sup> both of which cause extensive damage to and rearrangements of the meiotic chromosomes. Several groups of workers have been studying the potential teratogenic effects of the drug. As with other drugs, the time of injection during pregnancy seems to be of importance, and rats,<sup>13</sup> mice,<sup>14</sup> and hamsters<sup>15</sup> all show an increase of congenitally malformed fetuses when it is injected early in pregnancy. On the other hand, a comparison of the effects of L.S.D. and thalidomide on rabbit fetuses<sup>16</sup> failed to show a teratogenic effect of L.S.D., so that in this species at least it is not so powerful a teratogen as thalidomide proved to be.

It is becoming clear that many more carefully controlled studies are needed to compare the effect of L.S.D. with other drugs of known teratogenic and mutagenic potential before the effects of this potentially dangerous substance can be evaluated. Since it is taken illicitly by some people and is used in the treatment of psychiatric disorders, a most careful evaluation of its properties is essential. The same standards should be used to evaluate this drug as have been used to study ionizing radiation and other agents known to damage chromosomes and chromatids.

## Tumours of the Oesophagus

Carcinoma of the oesophagus presents an important, intractable, and discouraging problem. It is responsible for 25,000 deaths annually in Europe and accounts for some 5% of all carcinomas. Many aetiological factors have been blamed, including alcohol, tobacco, various nutritional deficiencies, malabsorption, and chronic irritation.<sup>1-4</sup> The association of post-cricoid carcinoma with the Plummer-Vinson syndrome in women is well established and the incidence of cancer complicating achalasia is high.<sup>5</sup> Less certain is the role

played by chronic reflux oesophagitis due to hiatus hernia<sup>6</sup>; but in a five-year survey of patients at the London Hospital with squamous carcinoma in the lower two-thirds of the oesophagus 12% had previous long-standing dyspepsia.<sup>7</sup> Men are affected more commonly than women (though most cases of cancer in the upper oesophagus occur in the latter) and the great majority of patients are between the ages of 60 and 70, the onset in women tending to be somewhat earlier.

Dysphagia is by far the commonest presenting symptom and demands rigorous investigation by barium studies and oesophagoscopy in every case. It ought never to be attributed to "functional causes" or labelled "globus hystericus." Sometimes a productive cough indicates lung infection caused by aspiration of food from the obstructed oesophagus. Pain, especially in the back, is usually a late and sinister symptom. Loss of weight does not necessarily spell cachexia, as in most other malignant conditions, but usually reflects semi-starvation and dehydration.

Spread of growth to the regional lymphatics and to neighbouring structures such as the bronchial tree, the aorta, and the vertebral bodies soon occurs,<sup>8</sup> so that at operation in one-third of the patients the carcinoma is irremovable and in two-thirds it has disseminated to a degree that renders lasting cure a forlorn hope.<sup>9-11</sup> The object of treatment in oesophageal cancer is therefore to palliate the misery of dysphagia rather than to aim at five-year survivals, and this can be achieved in the great majority of cases. Post-cricoid growths and neoplasms above the aortic arch are best treated by deep x-ray therapy,<sup>12</sup> though excision and replacement by a length of colon have a place in favourable instances.<sup>13</sup> In the lower two-thirds of the oesophagus wide resection of the growth is indicated, and continuity can be restored by use of the stomach, jejunum, or colon as the surgeon prefers, sometimes preceded by deep irradiation. In the past decade five-year survivals have approached 20%.<sup>14-16</sup> When the neoplasm cannot be removed it is bypassed, whereas if the patient is unfit for major surgery, or inoperability is manifest clinically, palliation can be achieved by the passage of a Mousseau-Barbin or some similar prosthetic tube.<sup>17</sup>

By one means or another, and in almost every instance, the patient should have restored to him the power to swallow.

<sup>1</sup> Dunlop, E. E., *Ann. roy. Coll. Surg. Engl.*, 1961, 29, 28.

<sup>2</sup> Hutt, M. S. R., and Burkitt, D., *Brit. med. J.*, 1965, 2, 719.

<sup>3</sup> Wright, J. T., and Richardson, P. C., *Brit. med. J.*, 1967, 1, 540.

<sup>4</sup> *Brit. med. J.*, 1966, 2, 718.

<sup>5</sup> Ingelfinger, F. J., *Gastroenterology*, 1963, 45, 241.

<sup>6</sup> Michel, J. O., Olsen, A. M., and Dockerty, M. B., *Surg. Gynec. Obstet.*, 1967, 124, 583.

<sup>7</sup> Wright, J. T., and Richardson, P. C., *Brit. med. J.*, 1967, 1, 540.

<sup>8</sup> Miller, C., *Brit. J. Surg.*, 1962, 49, 507.

<sup>9</sup> Le Roux, B. T., *Thorax*, 1961, 16, 226.

<sup>10</sup> Petrovsky, B. V., and Vantsian, E. N., *Surgery*, 1967, 62, 833.

<sup>11</sup> Adams, W. E., *J. thorac. cardiovasc. Surg.*, 1965, 50, 141.

<sup>12</sup> Smithers, D. W., *Ann. roy. Coll. Surg. Engl.*, 1957, 20, 36.

<sup>13</sup> Fairman, H. D., and John, H. T., *J. Laryng.*, 1966, 80, 1091.

<sup>14</sup> Zacho, A., and Fischermann, K., *Acta chirurg. scand.*, 1965, Suppl. No. 356, 121.

<sup>15</sup> Brain, R. H. F., and Reading, P. V., *Brit. J. Surg.*, 1966, 53, 933.

<sup>16</sup> Nakayama, K., *Chirurg*, 1962, 33, 14.

<sup>17</sup> Waddington, J. K. B., and Bickford, B. J., *Brit. J. Surg.*, 1962, 49, 522.

<sup>18</sup> Harrington, S. W., *Trans. west. surg. Ass.*, 1948, 56, 110.

<sup>19</sup> Harrington, S. W., and Moersch, H. J., *J. thorac. Surg.*, 1944, 13, 394.

<sup>20</sup> Calmenson, M., and Clagett, O. T., *Amer. J. Surg.*, 1946, 72, 745.

<sup>21</sup> Flavell, G., *Brit. J. Surg.*, 1953, 41, 238.

<sup>22</sup> Schmidt, H. W., Clagett, O. T., and Harrison, E. G., *J. thorac. cardiovasc. Surg.*, 1961, 41, 717.

<sup>23</sup> Flavell, G., *The Oesophagus*, 1963. London.

<sup>24</sup> Borrie, J., *J. thorac. Surg.*, 1959, 37, 413.

<sup>25</sup> Stener, B., Kock, N. G., Pettersson, S., and Zetterlund, B., *J. thorac. cardiovasc. Surg.*, 1967, 54, 746.