pital informed me that he had observed 71 cases of aplastic anemia in three years, 53 of which had been subject to follow-up; one of these had developed PNH. In the same period, nine cases of PNH had also been observed, five of them having been previously diagnosed as aplastic anemia. Dr. Tien-tse Hwang in Taipei, Taiwan, reported that he had observed 10–14 new cases of aplastic anemia annually, as well as seven cases of PNH at the two hospitals where he worked, one of them the large National Defense Hospital. Among the first 10 cases of hypoplastic anemia he had seen in 1966, one of them subsequently developed PNH. From these several observations, the factor of coincidence for the two apparently disparate conditions of aplastic anemia and PNH seems unlikely.

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## EXHIBIT C.—CHLORAMPHENICOL—A NEW WARNING

In one month recently, I saw 4 new cases of aplastic anemia. Although they ranged in age from 3 to 63, and came from different sections of the country, they had one common denominator: chloramphenicol had been used in the recent past for minor respiratory infections. There was no history of the use of other antibiotics or potentially toxic drugs and since the anemia and the other manifestations appeared a few months after the last administration of chloramphenicol, it seemed clear that this drug was responsible for the marrow aplasia.

In our recently studied series of aplastic anemia (seen within the past 3 years) 8 of 30 had received significant amounts of chloromycetin, almost invariably for minor infections. Of the most recent 10 cases of aplastic anemia, 5 had followed therapy with chloramphenicol. The tragic thing about all these seriously ill cases, most of whom died, is *that the drug need never have been given.*

It is becoming increasingly clear that chloramphenicol, an excellent broad-spectrum antibiotic, has antimetabolic effects as well—that is, it may injure the intrinsic "machinery" of certain rapidly proliferating cells, notably of the bone marrow. Thus, Rubin and associates, using radioactive techniques, demonstrated a depressant effect of chloramphenicol on erythropoiesis; this occurred in 5 of 15 subjects receiving ordinary doses and in all of 4 cases with cancer who were given unusually large doses of the drug.[1] In another study by Saidi and Wallerstein [2] 10 of 22 cases treated with chloramphenicol for various infections developed striking vacuolization of nucleated red cells in the bone marrow, associated with a maturation arrest phenomenon and marked reduction in blood reticulocytes. The possibility is present that these temporary changes could go on to complete or partially complete destruction of the bone marrow providing (a) that sufficient drug was used or (b) the patient became sensitized in some manner and was given a second course of drug therapy at another time. It is thus conceivable that both an immediate or direct effect as well as an indirect or hypersensitivity mechanism may be responsible for the marrow reactions seen.

Following the introduction of chloramphenicol in 1948 and the reports of the first cases of aplastic anemia between 1950 and 1952, many editorials and reports of special ad hoc meetings appeared. Evidently the medical profession was profoundly influenced; in any event, the sales of chloromycetin declined sharply, reaching their lowest level in 1954. This lull was short-lived. By 1958, there was a five-fold increase in the sales of the drug and by 1960, enough chloramphenicol was being distributed, and presumably used, in the United States to supply 3,732,416 persons with 10 Gm. courses of the drug! (These data were supplied through the kind cooperation of Dr. Harry Carnes, Parke Davis & Co., Detroit, Mich.)

To those of us who see cases of aplastic anemia following the use of various possible etiologic agents, chloramphenicol stands out as the most important single historical factor. To be sure, evaluation of histories and even of statistics relating to both the incidence of aplastic anemia and of chloramphenicol as an etiologic agent is difficult. Nevertheless the importance of the chloramphenicol-aplastic anemia relationship persists, and one must naturally be concerned with the possibility that an increased incidence in aplastic anemia may result as use of the drug increases so rapidly. Is the pharmaceutical house which introduced and for there can be no question that this respected company has gone to every effort popularized the use of chloramphenicol to be taken to task? This seems unfair to ferret out statistics of case reports, to carry out experimental work in various animals and even to note the effects of marrow transplantation in chemically induced aplastic anemia of monkeys.

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[1] Rubin, D.; Weisberger, A. S.; Botti, R. E.; and Storaasli, J. P.: Changes in Iron Metabolism in Early Chloramphenicol Toxicity, J. Clin. Invest. 37: 1286–1292 (Sept.) 1958.

[2] Saidi, P., and Wallerstein, R. O.: Effect of Chloramphenicol on Erythropoiesis. To be published.