R. COLMAN, M.D.
Hematology Research Laboratory
J. MINNA, M.D.
Department of Medicine
Massachusetts General Hospital
Boston, Mass.

ANEMIA AFTER CHLORAMPHENICOL

To the Editor: In the July 3, 1969, issue of the New England Journal of Medicine, Nagao and Mauer report on chloramphenicol-induced aplastic anemia in identical twins. The implication of the drug in this particular report, as in fact in any report, is, of course, speculative. Furthermore, the type of bone-marrow depression reported in these cases is unlike that usually associated with chloramphenicol toxicity or "allergy." The two common marrow depressive effects of this antibiotic are: related to dose of drug administered and usually occurring while the patient is receiving the drug and, most importantly, reversible; and not related to dose, supposedly extremely rare (estimates vary from 1:20,000 to 1:100,000) occurring in 75 per cent of cases *after* the drug has been discontinued, and most importantly, irreversible. In the editorial in the same issue of the *Journal* Dr. W. Dameshek does not make mention of this fact, although the dangers of this antibiotic are trumpeted. Perhaps, the time has come for us to swing the pendulum back a bit. Certainly, chloramphenicol should not be used without proper indication, but surely, this applies to any medication.

Chloramphenicol is a remarkably effective drug in life-threatening situations, with the tremendous advantage of not impairing renal functions. The "panic over the use of chloramphenicol" has had its beneficial effects, but probably has also had its deleterious effects. Ampicillin has been and still is being used as a substitute for chloramphenicol. The phrase "broad-spectrum penicillin" seems to have a magical lilt connoting safety and effectiveness.

Finally, little comment has been made in the American literature regarding the article by R. Holt in the Lancet (No. 7502, June 10, 1967) in which he states, "... there seems to be no recorded case in which marrow aplasia has followed administration of chloramphenicol by parenteral routes alone." Thus, I use chloramphenicol freely in life-threatening situations, administer it by the parenteral route only and sleep well at night.

JACK MENDELSON, M.D., F.R.C.P. (C)
Division of Microbiology and Infectious Diseases
Jewish General Hospital
Montreal, Quebec, Canada

The above letter was referred to the authors of the article in question, one of whom offers the following reply:

To the Editor: As stated in our paper, the development of aplastic anemia after chloramphenicol therapy is uncommon. However, the patient in whom aplastic anemia will develop cannot be identified. The purpose of our paper was to point out that genetic factors may predispose a person to such an anemia.

As stated by Dr. Mendelson, the evidence that the aplastic anemia in our cases was secondary to chloramphenicol is circumstantial, as in all reported cases. It is true that the aplastic anemia occurring two weeks to five months after cessation of chloramphenicol is frequently fatal. However, as pointed out in the papers by Yunis and Bloomberg[1] and by Best,[2] some patients do recover completely.

It may be true as suggested by Holt that aplastic anemia does not occur when chloramphenicol is administered by parenteral routes alone. However, that hypothesis remains to be proved. We agree with Dr. Mendelson that chloramphenicol should be used in life-threatening situations. However, we would reserve its use for the patients in whom no other drug of equal efficacy with less potential harm is available.

TAKESHI NAGAO, M.D.
Cincinnati, O.

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RHEUMATOID MANIFESTATIONS WITH HEPATITIS

To the Editor: In the Case Records of the Massachusetts General Hospital of the July 24 issue of the *Journal*, Dr. Kurt J. Bloch states: "The arthritis accompanying chronic, active hepatitis may resemble rheumatoid arthritis in its presentation and distribution. However, rheumatoid nodules apparently do not develop in these patients, and one does not find permanent deformity of the joints or signs of bone erosion on x-ray examination."

We are presently in the process of reporting a case of chronic active hepatitis associated with erosive rheumatoid arthritis and a biopsy-proved rheumatoid nodule. Although we believe this to be the first report of a rheumatoid nodule associated with chronic active hepatitis, erosive arthritis, although uncommon, has been well documented.[1-3]

THOMAS V. GEAGAN, M.D.
Formerly, *Chief Resident in Medicine*
St. Elizabeth's Hospital
RICHARD A. MATTHAY
Fourth-Year Student
Tufts University School of Medicine
JOHN A. BOLZAN, M.D.
Assistant Clinical Professor of Medicine
Tufts University School of Medicine
Boston, Mass.

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LIPSTICK AND LUPUS ERYTHEMATOSUS

To the Editor: I write as a dermatologist who would like to call himself a clinical immunologist by virtue of his interest in contact allergic dermatitis and patch testing.[1] An eczematous reaction caused by a chemical applied beneath an adhesive patch indicates delayed hypersensitivity to that chemical. When the evidence of the positive patch test clarifies the clinical situation, then the logic is simple: remove the chemical (i.e. allergen) from the environment, and the contact dermatitis (i.e. delayed hypersensitivity) will not occur.

"Persistent light reactions" may follow the application of halogenated phenolic compounds in soaps or ointments and the application of "Jadit," an antifungal ointment. The experimental observations of Willis and Kligman[2,3] and the clinical observations of Burry[4] and Burry and Hunter,[5] who have studied "persistent light reactions," supply evidence that these reactions are caused by the retention of chemicals within the skin over many years and the production of photodegradation products, the allergens, when the skin is exposed to sunlight. The ability of skin to retain a chemical that is broken down to an allergen and then causes delayed hypersensitivity may not be unique; perhaps other tissues in

the body can do the same thing. Chromates and dyestuffs, which are common causes of delayed hypersensitivity in the skin,[6] have been implicated as causes of intestinal carcinoma when they are ingested in food.[7] Might they not also cause hypersensitivity in the gastrointestinal tract, especially if the tract were capable of retaining them over long periods? Might not the benefit that follows colectomy in ulcerative colitis and bilateral nephrectomy in Goodpasture's syndrome[8] result from removal of chemicals retained within the colon and kidneys respectively?

Many drugs, including isoniazid, para-aminosalicylic acid, hydantoin, hydralazine and quinine, are capable of causing a syndrome indistinguishable from systemic lupus erythematosus.[9] Drugs are capable of causing many single immunologic reactions in different persons (for example, quinine can cause contact dermatitis, widespread drug rashes, photosensitivity drug rashes, thrombocytopenic purpura and systemic lupus erythematosus). Eosin can produce contact dermatitis and photosensitivity drug rashes[10] and must be the commonest photosensitizing chemical ingested by women and probably by men, since it is contained in lipstick. The ability of eosin to bind strongly with body tissue in vitro seems to be proved since it is one of the two most commonly used stains in the pathology laboratory. Can eosin be retained in vivo, and if so what happens to all that eosin licked off all those lips? Perhaps systemic lupus erythematosis, which often presents as a photosensitivity rash and is eight times more common in women than in men,[11] is caused by the retention of eosin, which acts as a persistent immunological trigger causing "autoimmunity." Might not other dyestuffs incorporated into food[12] be suspected sources of "autoimmunity"? Are the immunologic responses in systemic lupus erythematosus that have been so thoroughly investigated the result of primary causes as yet unrevealed?

JOHN N. BURRY

Hackney, St. Peters, South Australia

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L-DOPA TREATMENT TOO SUCCESSFUL

To the Editor: I thought that it might be of value to point out an interesting complication of L-dopa treatment. In the past three weeks, I have had three patients, ages 57, 65 and 81, who have all responded beautifully to L-dopa treatment and who subsequently fell and fractured their hips. All three of these fractures were located in the neck of the femur. These patients had previously not been very active and subsequently became quite active. One of the patients was playing football with his grandson at the time of the accident.

I think that it is of importance to point out that patients with Parkinsonism, because of their age and also because of their lack of mobility, are subject to osteoporosis more than others. When L-dopa frees them of their rigidity and akinesia, they tend to overdo it, and their bones cannot withstand the force.

I think it would be worthwhile to advise all patients on L-dopa to resume activities such as dancing and playing football gradually rather than do them suddenly.

JACK GREENBERG, M.D.
Gill House–Episcopal Hospital
Philadelphia, Pa.

CIRCUMCISION AND TONSILLECTOMY

To the Editor: Dr. Bolande[1] has questioned the motivation for these operations and suggests they may have degenerated into ritualistic surgery. I consider some distinction between the two operations necessary since, when performed neonatally, circumcision is normally prophylactic whereas, performed subsequently, circumcision like tonsillectomy is normally therapeutic. The points raised by Dr. Bolande are extremely important since Cansever[2] has shown that circumcision around the phallic stage is perceived by the child as an act of aggression and castration and that it has a detrimental effect on his functioning and adaptation, particularly on his ego strength. Although I believe this to be true of any operation at this age, it has a special relevance to circumcision and tonsillectomy since the conditions promoting their performance are generally evanescent or amenable to alternative treatment.

I cannot accept that the parent is primarily responsible for their performance. The prime mover is the physician, who has come to be regarded in modern society almost as a high priest, Flower's superior or revered person. The natural inclination of the parent is to defer to the judgment of his or her medical adviser, and the import of this is reflected in the findings of Patel[3] in Canada and Fredman[4] in Australia regarding the influence of the physician's own attitude to circumcision on its frequency in his infant patients. This influence of the physician is even more dramatically illustrated by the situation in Darmstadt Municipal Hospital, Germany, where, as the result of a change in policy, circumcision of the newborn rose from nil to 80 per cent virtually overnight.[5]

Regarding the origins of circumcision, Morrison,[6] in an admirable disposition, compared its practice in Australia among the aborigines and the subsequent white settlers. This can leave little doubt that it did originate as preventive medicine as a result of environmental factors and that it subsequently became overlaid with mystical rites as a means of ensuring its observance. The original reasons have been forgotten, and the meaning transferred to the actual rite, this applying in a modern civilized society like a primitive one, as Dr. Bolande remarks. In determining one's attitude, one must examine how far these original reasons have been superseded lest one throw the baby out with the bath water.

The situation in countries where neonatal circumcision is not or, as here, is no longer practiced could be a reasonable guide, but unfortunately the evidence is conflicting. Øster,[7] in a comprehensive study of Danish children, found only the odd one who required circumcision, but on the other hand Schoberlein,[5] in Germany, where likewise there had been no tradition of circumcision, found on routine examination of 3000 young soldiers that 8.8 per cent required the operation for acute phimosis, with a substantially greater number for whom it would have been beneficial. He also noted a remarkable lack of preputial hygiene and an almost total ignorance about the subject irrespective of class. Saitmacher[8] described a similar situation among adolescents. Osmond,[9] here in England, had earlier reported like findings among young soldiers to those of Schoberlein, and it is interesting that, though one third of those examined had been circumcised, 7 per cent still required the operation, suggesting that selec-