Donohue (1941) has described perivascular demyelination, similar to that seen in other cases of post-infective encephalitis, when he reported the pathology of a case of fulminating mumps meningo-encephalitis. Gordon (1927) experimentally produced mumps encephalomyelitis in a monkey (*M. cynomolgus*), and noted a cerebrospinal fluid reaction similar to that seen in the cases described here. He also described histological parotitis at necropsy in four cases of encephalitis lethargica (Gordon, 1913). Armstrong *et al.* (1936) similarly demonstrated the virus of choriomeningitis in the testes of experimentally infected monkeys.

There are authenticated cases of orchitis (Humphries, 1947) and pancreatitis (Box, 1946) as the only signs of mumps. We may therefore be but guessing at the tissue predilections of virus organisms. It may well happen that cases loosely described as aseptic meningitis may in reality be mumps meningo-encephalitis. If, however, after study of the other manifold manifestations of mumps it is considered that this virus infection is generalized and apt to influence any tissue—even the foetus *in utero* (Humphries, 1947)—then it is quite understandable that the central nervous system can at times be affected too, and possibly in preponderance. Thus it would no longer be necessary to postulate a neurotropic virus but rather one which settles where it will, and, depending on the speed of immunity production, the salivary glands, central nervous system, pancreas, ovaries, testicles, or pericardium may one or all produce clinical signs of virus inflammation.

Summary

The literature concerning the central nervous system manifestations of mumps is reviewed.

Fourteen cases of mumps meningo-encephalitis are presented, six of which occurred before other signs of mumps developed.

The place of the neurological signs of mumps in the picture of the disease is discussed, and it is suggested that, being a general infection, central nervous types of the disease are apt to occur more by accident than because the virus is necessarily essentially neurotropic.

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LEUCOCYTE COUNTS IN THE PREVENTION OF DRUG AGRANULOCYTOSIS

BY

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Himsworth (1948) stated that he and Morgans (1947) had come to the conclusion that frequent blood counts for the early detection of agranulocytosis during treatment with thiouracil are worse than useless, because agranulocytosis develops like a bolt from the blue, and a normal count may impart a quite unjustifiable sense of security. This has long been known in the case of the sulphonamides, but the evidence has been generally disregarded, and leucocyte counts for purposes of prophylaxis are still considered desirable. Roberts (1948) and Hendry (1948) have drawn attention to the greatly increased demands being made on clinical pathological departments of hospitals, and leucocyte counts, requested under the mistaken impression of their value in the prevention of agranulocytosis, constitute an unnecessary and wasteful part of such demands.

I drew attention to the failure of serial leucocyte counts during sulphanilamide administration either to give warning of an impending agranulocytosis or to prevent a fatal outcome (Young, 1937). Later I collected evidence supporting this observation (Young, 1944). On the other hand, Britton and Howkins (1938) carried out leucocyte counts during 14 days of sulphonamide treatment in 50 patients, and found that the polymorphs fell during treatment in 46% of cases—in 10% to fewer than 2,000 per c.mm—but they did not observe agranulocytosis. Also Bigler *et al.* (1938) carried out counts in 33 persons during short courses of sulphonamide treatment, and concluded that sulphonamides seemed to cause depression of white blood cells even to a point at which leucopenia developed, but agranulocytosis did not occur with this depression.

It might be anticipated that leucocyte counts would be useful in the prophylaxis of agranulocytosis in two ways: (1) in preventing the occurrence of agranulocytosis, and (2) in reducing case mortality through earlier diagnosis.

Influence of Counts on the Occurrence of Agranulocytosis

It has been assumed that the detection of a drop in the leucocyte count to a leucopenic level during treatment would enable agranulocytosis to be averted by stopping administration at this stage, and it has been claimed that this has been achieved (Hohmann, 1938). Plum (1937), by administering amidopyrine to patients who had recovered from agranulocytosis due to the same drug, showed that the changes in the marrow are well established before the peripheral blood gives any warning, and that, although administration of the drug was stopped long before this warning in the blood, agranulocytosis followed. His experiments, and other evidence (Sheket and Price, 1939; Agranat *et al.*, 1939; Filler, 1941), indicate that when a leucopenia is due to an imminent agranulocytosis the latter will follow whether the drug is stopped or not. If a rise in granulocytes occurs immediately after administration ceases the condition merely represents the mild leucopenia which occurs in about 50% of persons, as demonstrated by Britton and Howkins (1938) and Bigler *et al.* (1938) with sulphonamides.

That such a leucopenia does not proceed to agranulocytosis is readily demonstrated by continuing the administration of the drug. Such a test case is the following, in which thiouracil was given for the treatment of thyrotoxicosis.

Before treatment was started the blood showed a polymorph count of 3,000 per c.mm. in a total leucocyte count of 5,600. After 14 days' treatment the count had fallen to 1,480 polymorphs in a total count of 3,900. At this stage, instead of suspending treatment, the dose of thiouracil was doubled. Four days later the counts were the same, the polymorphs being 1,587 and the total leucocytes 4,100. At the end of a further six days' treatment the polymorph count had risen to 3,538 and the total leucocytes to 6,100, restoration to the pre-treatment level having ensued in spite of the continued administration of the higher dosage.

If such a leucopenia is to be used as an indication for stopping treatment it not only seems to be an unreliable indicator but may be so misleading that it results in patients being deprived unnecessarily of the benefits of treatment.

Filler's (1941) case strikingly demonstrated the failure of leucocyte counts in the prevention of agranulocytosis. The case was one of staphylococcal septicaemia treated with sulphamethylthiazole. After the blood culture had become sterile, pyrexia was still present and drowsiness was noted for the first time. There was no leucopenia at this period, but owing to the suggestion of toxicity the drug was stopped. Six days later polymorphs had completely disappeared from the peripheral blood, so that, although treatment had ceased before there was any warning leucopenia, agranulocytosis was not prevented.

Influence of Leucocyte Counts on Mortality

Although leucocyte counts are generally misleading as indicators of impending agranulocytosis, it might be anticipated that serial counts, by bringing about cessation of the offending drug at the earliest possible moment, would lower mortality in comparison with cases in which no counts were made.

To test this assumption the available data relating to 74 cases of sulphonamide agranulocytosis were extracted from the literature and are presented in the Table.

Table Showing Leucocyte Counts and Mortality

No. of Counts:	0	1-14	1-3	4-14
No. of recovered cases	14	19	14	5
No. of fatal cases	16	25	16	9
Case mortality per cent	53	57	53	64
Observed difference per cent ..		4		11
2 x standard error of difference ..		23.5		32
Significance of difference ..		Nil		Nil

Two comparisons are made: first, between cases having no counts and those having one or more; secondly, between those having one to three counts and those having more than three. The latter are rather few in number, but in no group was any significant difference in case mortality demonstrated. While the data may not be sufficient to establish the absence of any influence of leucocyte counts on case mortality, they show that the assumption generally made that they will do so is not justified on the available evidence, at least in regard to the sulphonamides. Individual cases illustrate how completely they can fail. In one of my own cases (Young, 1937) treatment was stopped on the day after a count which showed no drop in polymorphs, so that even if a reduction had been demonstrated on the following day the drug would not have been stopped sooner, yet the patient died. In the case of Sheckel and Price (1939) five counts in the six days preceding agranulo-

cytosis failed to avert a fatal outcome, although the drug was stopped when the leucocytes fell from 12,500 to 8,500 per c.mm. Morgan and Detweiler (1939) described a case in which 14 counts were made during 19 days' treatment, but again death occurred. Other cases providing similar evidence are among those enumerated in the table, references to which, with individual data, are given by Young (1944).

Discussion

The evidence, both experimental and clinical, indicates that in drug agranulocytosis the condition is inaugurated in the bone marrow some time before granulopenia occurs in the peripheral blood, and the information given by the latter is too late for prophylactic purposes. Plum's (1937) experiments with amidopyrine showed that the formation of granulocytes ceased at its earliest stage, but that the marrow granulocytes already formed continued to develop and so sustained the numbers in the peripheral blood for some days after the condition had been established in the marrow.

The bone-marrow changes found in sulphonamide agranulocytosis have been variously described as absence, reduction, maturation arrest, and aplasia of neutrophil granular cells, but the term "maturation arrest" is not justified, as it has been based only on single examinations which cannot show whether the picture is static or changing. As indicated above, Plum showed that there was no maturation arrest in amidopyrine agranulocytosis.

Rubinstein (1944) made serial marrow examinations in a case of thiouracil agranulocytosis during recovery. He showed that the return to normal of the marrow preceded that of the peripheral blood, the polymorphs in the latter reaching the pre-treatment level some time between the sixth and nineteenth days after the marrow count was normal. These observations again indicate a considerable time lag between the marrow and the peripheral blood, and agree with Plum's findings with amidopyrine that marrow examination gave earlier information than did the blood.

Beck (1933) recorded that the myeloid bone marrow in agranulocytosis might be aplastic, normal, or hyperplastic, and this variability in the marrow findings has caused some confusion regarding the basis of the condition. A type of agranulocytosis occurs which is probably due to cell destruction rather than failure to produce granulocytes, but, so far as is known, this type does not seem to be produced by drugs. The finding of numerous granulocytes in the bone marrow has been reported in cases due to various drugs, including at least one due to sulphonamides (Rosenthal and Vogel, 1939). It is probably significant that this sulphonamide case was the only one to recover among those in which the marrow was examined in the series studied by Young (1944), the others all showing various degrees of aplasia.

From an examination of available data (Dameshek, 1944; Young, 1944) it seems likely that the variations reported in the marrow in drug agranulocytosis generally are due to variations in the state of marrow recovery at the time of examination. The marrow has most often been examined post mortem, and, death being as a rule due to bacterial invasion and not directly to the state of the marrow, all stages of recovery in granulocyte production may be present at the time of death. A single examination of the marrow may therefore be misleading in regard to the nature of the condition, which, when due to drugs, usually appears to be aplastic in type.

Instead of leucocyte counts during treatment with thiouracil, Himsforth *et al.* (1947) recommend that every patient should be told that if he develops a sore throat

or fever he must discontinue the drug and report to his doctor. The same procedure might be applied in the prolonged sulphonamide administration employed in rheumatism prophylaxis. For other cases of sulphonamide administration, limitation of the period of treatment to a week or ten days is probably the best method of prophylaxis, and seems to have almost eliminated agranulocytosis due to this group of drugs. Amidopyrine agranulocytosis is readily avoided, as this drug is unnecessary and should no longer be used.

Summary

No evidence has been found that serial leucocyte counts during the administration of agranulocytosis-producing drugs either prevent agranulocytosis or reduce case mortality.

The reason for this failure is found in the bone marrow, where the condition can become fully established before the peripheral blood gives any warning.

Reliance on leucocyte counts is undesirable, as they may give rise to a misguided sense of security which may prevent the adoption of more useful measures.

Leucocyte counts for purposes of prophylaxis also constitute a waste of time in clinical pathological departments of hospitals, and may mislead clinicians into stopping the administration prematurely, so unnecessarily depriving patients of the benefits of treatment.

Other methods of dealing with drug agranulocytosis are briefly mentioned.

I am indebted to Dr. J. K. Rennie for clinical data. Much of the material in this article is taken from a thesis accepted by the University of Edinburgh for the degree of M.D.

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Information about the hospital services in the United States is summarized in a report published in the *Journal of the American Medical Association* (May 7, 1949, p. 23). The present bed capacity is 1,423,520, and the average daily number of patients occupying hospital beds during 1948 was 1,217,154. Between 16 and 17 million patients were admitted to hospital during the year. The greatest increase in service compared with past years was in the general hospitals. The average daily number of patients in mental hospitals was 664,399: thus nearly 55% of the occupied hospital beds were utilized for psychiatric care. The tuberculosis hospitals contained about 5% of the total hospital load. The average length of stay in general hospitals fell from 11.4 days in 1947 to 10.5 in 1948. There are now 807 hospitals approved for the training of interns and 1,140 for the training of resident physicians. The accredited schools of nursing education, which total 1,163, enrolled 100,174 student nurses in 1948.

TORSION OF NORMAL FALLOPIAN TUBE

BY

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Torsion of the normal Fallopian tube when first encountered strikes one as being rare enough to warrant a little excitement. On looking at the tube and its mesentery during operative work in the abdomen it is hardly conceivable that the tube itself should undergo torsion without involving the neighbouring structure of the ovary: with its broad pedicle it would seem impossible that it could so twist on itself as to give rise to urgent symptoms.

Case Report

A 2-para aged 24 was admitted to the maternity unit of the Ayrshire Central Hospital on Dec. 7, 1947. The elder child was 2½ years and the younger 8 months. The family history showed nothing of importance. The husband was alive and well. The patient had been feeding the baby until three weeks before admission to hospital. She stopped on account of an attack of pain in the left iliac fossa and slight uterine bleeding. This was the first sign of uterine bleeding since the birth of the baby, and she was sent to hospital by her doctor as a case of threatened abortion or of subinvolution.

On admission the temperature was 99° F. (37.2° C.), pulse 124, respirations 20, B.P. 120/80 mm. Hg; blood Rh-negative; O(iv); W.R., negative; urine, N.A.D.; chest, heart, and lungs, N.A.D. On vaginal examination a small tender mass was felt behind the uterus, which was slightly enlarged, retroverted, and tender.

After admission there was no further uterine bleeding, so the differential diagnosis rested between ectopic gestation and an inflammatory condition of the tubes. During the next three days there was a slight rise in temperature, and a course of penicillin of 1,000,000 units was given. An Aschheim-Zondek test, which had been taken on admission, was now shown to be negative, and as the patient's temperature had settled she was examined under general anaesthesia. The previous findings were confirmed and the provisional diagnosis of tubal mole made.

Operation.—On Dec. 16 the abdomen was opened through a Pfannenstiel incision. A small mass surrounded by adhesions was found in the pouch of Douglas. When the adhesions were freed the mass was found to be the left tube with three clockwise twists in it. It was removed, leaving the ovary untouched, and the stump was buried in the broad ligament. Appendicectomy was performed and the abdomen closed. The patient was ambulatory by the third day and was discharged from hospital on Dec. 27, 11 days after the operation.

The specimen would at first suggest an atypical tubal pregnancy which had undergone torsion. Section showed no evidence of pregnancy, and microscopically no cells suggestive of decidua or chorionic elements could be found. This, after consideration of the patient's symptoms and history in retrospect, supported the diagnosis of simple torsion of the tube.

Discussion

The standard midwifery textbooks make no mention of this entity, but after reviewing some of the literature it was perceived that it was not really rare. Bland-Sutton (1890) reported the first case, and since then many others have been published. In the majority there has been a history of a diseased condition of the tube—hydrosalpinx, etc. Darner (1926) states torsion of the undiseased tube is less common, particularly in the virgin. French authors, in particular Regad (1933a, 1933b), have referred to a syndrome,