The diagnosis of subarachnoid hemorrhage usually presents no great difficulty. However, in the period immediately following the hemorrhage it is usually impossible to determine whether the bleeding is continuing or has ceased. Furthermore, for some time after the original episode, it is difficult to detect minor recurrences of bleeding. Conventional methods of clinical observation and examination of spinal fluid seem inadequate to determine accurately the course of subarachnoid bleeding.

In order to institute further diagnostic and therapeutic procedures at the optimal moment, it may be of considerable value to be able to determine whether bleeding has stopped or is continuing steadily or intermittently. Much of the difference of opinion that exists regarding the advisability of performing surgical diagnostic procedures, such as arteriography in cases of subarachnoid hemorrhage and the proper time for instituting such procedures, arises from a lack of precise information concerning the status of the bleeding. That opinions on these matters actually do vary widely will be evident from a few examples chosen from the literature on subarachnoid hemorrhage.

Walker, in an editorial on subarachnoid hemorrhage, stated: "A brief survey of the literature on the subject of subarachnoid hemorrhage and aneurysms will convince anyone that most of the data now available is so incomplete and biased that it only compounds the confusion of an already complex issue." He also stated that "indications and contraindications for surgical diagnostic and therapeutic procedures to control a bleeding aneurysm and to prevent future hemorrhages have to date not been clearly defined."

Silver advocated that all patients suffering intracranial bleeding be subjected to prompt cerebral angiography. He further advised that this examination be carried out as soon as possible after the episode of bleeding, and treatment for the lesion be instituted as soon as practicable. His conclusions were based on an analysis of 100 consecutive cases of intracranial bleeding. Rowley, reporting on a mixed analysis of 157 cases of spontaneous sub-
arachnoid hemorrhage, regarded patients with spontaneous subarachnoid hemorrhage as surgical emergencies and recommended angiography be performed within 48 hours of the onset of the hemorrhage, to be followed by surgical therapeutic measures if the aneurysm is located. On the other hand, he advocated conservatism when a patient presents several weeks to months following a subarachnoid hemorrhage.

Magladery\(^1\) analyzed 235 patients with proven subarachnoid bleeding who were admitted to the Johns Hopkins Hospital during the years 1947–1954. He concluded by stating that his clinical material does not support the view that presently available surgical means of intervention offer any improvement over the current conservative approach. In speaking of angiography, Magladery made an analysis of the 90 patients, out of the whole 235, who had angiography. He stated that 53 per cent revealed no evidence of arterial aneurysm, arteriovenous malformation, or angioma. He further stated that the incidence of “positive” examinations was lowest when the procedure was performed during the first 7 days, adding that the chances of demonstration were found to be about 1 in 3 if done during that time; thereafter, he added, the odds were about equal. He stated that the mortality rate of the 235 patients was 46 per cent in those conservatively treated and 65 per cent in those operatively treated, surgical measures yielding an added mortality of 19 per cent. However, when he tabulated the mortality in a smaller group of 95 normotensive patients under 60 years of age, he found a 29 per cent mortality rate with conservative treatment and 65 per cent with surgical treatment, disclosing a disparity of 36 per cent.

The aforementioned sampling of the pertinent literature stresses the need for further fundamental information concerning patients with subarachnoid hemorrhage.

In an effort to provide a simple reliable method for more accurately following the course of subarachnoid hemorrhage, a new technique was developed. The procedure depends on the demonstration that intravenously injected red blood cells tagged with chromium 51 can be detected promptly in the spinal fluid when active subarachnoid bleeding is taking place.

METHOD

It is now a simple matter for any medical isotope laboratory to tag a patient’s red blood cells with chromium 51 within 1 hour. Some hospitals store group O blood, already tagged with chromium 51.

For control purposes, 15 normal individuals were studied. In each of these, 50 cc. of blood were withdrawn, tagged with chromium 51 and reinjected intravenously. Five cc. of spinal fluid were obtained 2 hours later and 24 hours later. The “specific activity” (radioactivity) of these samples of spinal fluid was immediately measured.

In 5 subjects to whose blood 100 microcuries of chromium 51 had been added, the specific activity of the spinal fluid was found to range between 4\(\frac{1}{2}\) and 5 per cent above the background activity (Fig. 1).

In the other 10 individuals, to whose blood 200 microcuries of chromium
51 had been added, the specific activity of the spinal fluid was found to range between 0 and 12 per cent above the background activity (Fig. 1).

The specific activity of the spinal fluid in normal subjects reached its highest level within 24 hours after injection of red cells tagged with chromium 51, and thereafter gradually diminished. The specific activity of the spinal fluid of 4 patients with subarachnoid hemorrhage, who were tested when no active bleeding was evident, yielded a curve identical with that of the controls; peak levels were observed within 24 hours and gradually diminished thereafter.

An estimate of the sensitivity of the method was obtained from the following experiment:

The peripheral blood taken from patients 24 hours following the injection of 200 microcuries of chromium 51, was introduced in fractionated amounts from 1/4 cc. to 2 cc. into a series of flasks containing 180 cc. of normal saline. The 180 cc. volume was chosen as this represents the average maximum amount of cerebrospinal fluid present in the subarachnoid space and ventricular system. When only 1/4 of a cc. of peripheral blood was added to the 180 cc. of saline and the radioactivity of 5 cc. of this 180 cc. volume was determined, a 20 to 65 per cent increase above background was obtained.

CASE REPORTS AND LABORATORY DATA

The following observations were made on 8 patients with spontaneous subarachnoid hemorrhage; 4 received blood tagged with 100 microcuries and 4 received blood tagged with 200 microcuries of chromium 51.

The time interval between onset of symptoms and transfusion of tagged cells in the 8 patients with spontaneous subarachnoid hemorrhage varied from 1 1/2 hours to 3 days. In referring to these patients, the term "active bleeding" will be used to denote a significant increase of chromium 51 in the spinal fluid.
CASE REPORTS

Case 1. C.F.S. (Fig. 2) was seen 3 days following the onset of symptoms and was “actively bleeding” at the time of admission. Increased bleeding was evident on the 4th day, which was 1 day after admission. This “active bleeding” was not detectable clinically. Five weeks after admission bleeding recurred; 200 microcuries of chromium 51 were reintroduced intravenously and “active bleeding” was immediately in evidence, and continued for 1 day following this second hemorrhage. Again his persistent bleeding was not detectable clinically. Nine days following the second hemorrhage, during which time he progressively improved, he bled for the third time with immediate cessation of both respiration and cardiac action. At autopsy a ruptured aneurysm of the basilar artery was found.

Case 2. C.A. (Fig. 3), seen 18 hours following the onset of symptoms, showed evidence of “active bleeding” 2 hours later. One day later, there was evidence of increased bleeding. Four days after tagging there was evidence of recurrent bleeding, as shown by a rise in the specific activity of the spinal fluid, and perhaps again on the
The degree of "active bleeding" and the clinical course could be correlated for the first 2 days. After this, the clinical picture improved, but there was no correlation between recurrent "active bleeding" and progressive clinical improvement.

Case 3. T.H. (Fig. 4) was seen 2.5 hours after hemorrhage which, by history, was the second hemorrhage; the original hemorrhage had occurred 17 days previously. At no time during his clinical course was there isotopic evidence of "active bleeding." The type of curve shown in Fig. 4 was also obtained in the 15 control subjects.

Case 4. B.E.S. was seen 1.5 hours after hemorrhage. No discernible "active bleeding" was in evidence at any time during his course, which was one of progressive improvement. He had a convulsive seizure on the 2nd day, at which time there was no isotopic evidence of "active bleeding." This patient, by history, had had a previous hemorrhage 12 days prior to admission.

Case 5. R.M.D. (Fig. 5) was seen within 1 day after hemorrhage. He had a left central facial paresis and a left hemiparesis. His clinical course was one of gradual improvement. At both 16 hours and 3 days after injection of tagged red cells, there was evidence of "active bleeding"; here again, the period of probable "active bleeding" could not be correlated with his progressive clinical improvement. This patient is classified as a probable "active bleeder" because of his isotope uptake.
precise classification of this patient can be made only after interpreting the curves of a greater number of patients.

Case 6. H.V. was seen 1½ hours after the onset of hemorrhage. "Active bleeding" was in evidence 3½ hours following the hemorrhage, and persisted for 1 day following the hemorrhage. Her history was one of sudden right orbital pain, vomiting and precipitous coma. On the following day, respiration ceased and her blood pressure was unobtainable. She was placed in a respirator and given noradrenalin on which she was sustained for a period of 6 days. The patient expired on the 7th day. At the time she was placed in the respirator, isotopic evidence of subarachnoid bleeding was still present. However, from this point on there was no further evidence of "active bleeding," up to and including the day the patient expired.

Case 7. E.H. was first seen 6 hours following hemorrhage, and at 8 hours following hemorrhage there was no evidence of "active bleeding." There was no evidence of "active bleeding" on successive days, during which time the patient progressively improved. Angiography revealed an aneurysm of the left middle cerebral artery which, however, was ipsilateral to this hypertensive patient's hemiparesis.

Case 8. J.G.H. was seen 3 days following hemorrhage, at which time there was no isotopic evidence of "active bleeding." There was no evidence of "active bleeding" at any time during his illness. The clinical course was one of progressive improvement.

Comment. In each patient the isotope level in the spinal fluid was compared with the actual count of the red blood cells per c.mm. in the spinal fluid, with the following results.

In Case 1 the most profuse bleeding was indicated on the 6th day on the basis of a rise in the count of red blood cells in the spinal fluid, whereas the height of "active bleeding" as indicated by the isotope level occurred at 15 hours, with a subsequent steady decrease. When the patient had a recurrent hemorrhage at 5 weeks, a fall in the count of red blood cells in the spinal fluid suggested decreased bleeding on the 2nd day, whereas the isotope level reflected "active bleeding" continuing on the 2nd day.

In Case 2 there was a close correlation between the isotope level and the count of red blood cells in the spinal fluid.

In Case 3 the count of red blood cells in the spinal fluid increased 24 hours after admission, suggesting "active bleeding," whereas the isotope level yielded no evidence of "active bleeding" at any time.

In Case 4 interpretation of the count of red blood cells in the spinal fluid was inconclusive, when the isotope level evidenced no "active bleeding."

In Case 5 the count of red blood cells and isotope level corresponded closely.

In Case 6 a decrease in the count of red blood cells in the spinal fluid on the 2nd day could be interpreted as evidence of decreased bleeding, whereas, the isotope level reflected "active bleeding" at that time.

In Case 7 a progressive rise in the count of red blood cells in the spinal fluid suggested "active bleeding" for 3 days; the isotope level at no time yielded any evidence of "active bleeding."
In Case 8 the count of red blood cells in the spinal fluid suggested “active bleeding” for 1 day and 2 days later suggested a recurrence of bleeding. The isotope level revealed no evidence of “active bleeding” at any time.

DISCUSSION

A normal control series of 10 patients who received 200 microcuries of radioactive chromium 51 intravenously, yielded a maximum uptake of 12 per cent chromium 51 in the spinal fluid 24 hours later. Five control patients who received 100 microcuries of chromium 51 yielded a maximum uptake of 5 per cent chromium 51 in the spinal fluid at the 24-hour period.

It is our suggestion that a dose of 200 microcuries of chromium 51 be given intravenously to reduce the error of interpretation of active intracranial hemorrhage. It might be advisable to do the spinal puncture simultaneously with the intravenous injection of the tagged red blood cells, and then obtain spinal-fluid samples over a period of the first 10 minutes rather than 2 hours later.

By utilizing this procedure in patients with subarachnoid hemorrhage, one can determine whether or not bleeding into the subarachnoid space has been arrested, is continuing, increasing or is continuing intermittently. One finds in this small group of cases, isotopic evidence of bleeding for 2 to 4 days following the onset of symptoms, as well as isotopic evidence of intermittent bleeding. There was no correlation between clinical improvement and continued “active bleeding” as evidenced by uptake of the isotope in 3 active bleeders, and in the 1 probable active bleeder.

What we can gain by knowing whether or not there is active bleeding, rests with further experience, acquired only through the study of more patients. At this point, one can only speculate. We may be able to improve our timing for arteriography. Our judgment may be improved in separating those patients who should be treated early surgically, from those who should be treated medically, thus decreasing the mortality rate of those patients in whom the danger would be increased by early surgical measures, while improving the chances of cure for those requiring early surgical treatment.

This method may also afford evaluation of various forms of medical management. Curves of isotope levels derived from patients with various causes of spontaneous subarachnoid hemorrhage would have to be studied to determine whether or not independent patterns actually exist.

The cause of subarachnoid hemorrhage was a ruptured arterial aneurysm in 2 of the 3 active bleeders; both these patients expired. In the third active bleeder no aneurysm was found. In the probable active bleeder no aneurysm was found. In the 4 patients in whom there was no isotopic evidence of active bleeding, no demonstrable aneurysm was found, except in 1 case, in which the aneurysm was ipsilateral to the hemiparesis. Vertebral angiography was done in only 1 of 8 patients. The patients who showed no evidence of active bleeding all survived. The patient who was a probable bleeder also survived.

In this small series of patients the presence of isotopic evidence of active
bleeding was unfavorable prognostically, whereas the absence of such evidence was favorable prognostically.

There was no correlation between the count of red blood cells in the spinal fluid and the uptake of isotope in the spinal fluid in 6 of the 8 patients. On an experimental basis, approximately 2 drops of blood tagged with chromium 51 dispersed into the cerebrospinal fluid yielded a 20 to 65 per cent increase of radioactivity above background.

Radioactive chromium 51 was not responsible for any deleterious effects upon the central nervous system or upon the meninges that could be determined clinically, or by examination of the count of white blood cells and response of protein in the spinal fluid, or by actual gross and histologic studies of the meningeal tissues, brain, and spinal cord of the 2 patients who died. The half-life of chromium 51 is 26 to 28 days.

This procedure is being presented as an additional diagnostic measure. The experience of other investigators utilizing this procedure should prove of distinct value in the accumulation of sufficient data to arrive at definitive conclusions.

SUMMARY

1. A new method has been described to detect the presence of “active bleeding” into the cerebrospinal fluid.

2. Observations of patients with subarachnoid hemorrhage whose blood has been tagged with chromium 51 have been tabulated, graphically demonstrated, and discussed.

REFERENCES