REPORT OF PROGRESS - NsG 516

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To: National Aeronautics and Space Administration
Office of Space Sciences and Applications
Office of Research Grants and Contracts

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This report is in the nature of a statement of progress to date. For reasons that will be evident below, a conclusive report on the project is not possible at this time. Work is continuing because at this point we are just beginning to obtain data which are meaningful with respect to the original aims of the proposal. But these are not yet the kinds of data we set out to acquire. Another year is necessary in order to obtain information acceptable for general publication. This will enable us to make the best use of experienced, trained personnel and of our experiences with the instrumentation.

I. Experimental Plan. The plan of experimental attack was, and still is, as follows:

A. To determine in a preliminary way the reliability, error of measurement and operational characteristics of the specific instruments being used, e.g., the electromagnetic flowmeter and its probes, the cardiac output computer, the dye densitometer for cardiac output, and associated recorders for the foregoing. These observations were to be made using flow system models with outdated banked human blood, stored frozen dog artery segments, and acute studies on anesthetized dogs.

B. To install, aseptically, flow probes on the renal artery and/or ascending aorta of dogs with a view toward long term, but periodic, observation of blood flow. Data from the flowmeter was to be checked against data from dye cardiac outputs and renal clearance estimates of blood flow.

C. Assuming success of the above steps, flow probes were to be implanted aseptically on renal vessels and ascending aortae of monkeys to determine the reaction of the animals as well as the particular blood vessels to these procedures. The animals were to be semi-restrained in a sitting position and in some instances subjected to controlled environmental conditions of heat and light. The effects on blood flow and cardiac output of struggling by the animal against its restraints, and of orienting it in space in various ways, while still confined, were to be studied.

II. Methods. Blood flow was determined by means of a square-wave electromagnetic blood flowmeter (Carolina Medical Electronics, Model 301) with recording directly on a Gilson Medical Electronics, Model M5P, direct-writing oscillographic recorder or with immediate display on a Tektronix oscilloscope, type 564. (For data storage a Sanborn, model 2007, tape recorder will be used when available. A new Ampex tape unit was installed six months after original delivery to correct a defect. The new unit is not yet matched to other instrumentation.)

Whole body blood flow (cardiac output) was determined by the well-established dye dilution procedure. Indocyanine green (Cardio-Green of Hynson, Westcott and Dunning) was injected as a single quick slug (1 mg dye in 0.5 ml volume in a weighed syringe), by filled catheter, into a large vein near the heart, and immediately blood withdrawal was started by catheter, from a large central artery through a photoelectric densitometer (Gilson Medical Electronics, Model DTL). Blood withdrawal was by a motor operated syringe (Harvard Apparatus Co.) with a rate of approximately one ml per sec. Output of the densitometer was sufficient to drive a servo amplifier (Gilson Medical Electronics Model SE 21) and recorder capable of inscribing a complete dye time-concentration curve on 20 cm recording paper. In turn, the signal from

the servo amplifier was fed into a Sanborn, Model 130, cardiac output computer. (The latter instrument is a relatively recent development and, to our knowledge, it has not been applied in this manner heretofore. Its purpose here was to provide frequent successive determinations of whole body blood flow by the dye dilution method and to enable us to check the operation of implanted aortic flow probes in the future. Moreover, its application along with the servo-recorder, which inscribes a dye curve, provided an additional check. The Sanborn cardiac output computer is essentially a direct readout digital volt meter whose circuitry is designed to integrate the dye curve. It displays a figure which, after proper system calibration, can be used to calculate quickly the mean dye concentration during the first circulation of the dye slug and, hence, the cardiac output.)

Two elementary models were constructed for testing and indoctrination purposes. One was a gravity flow system by which blood from an elevated reservoir (seven feet above the flow probe) flowed through an electromagnetic probe. This system was used to check out amplifier and probe characteristics and to check directly flow measurements; blood flow into a graduate cylinder was timed with a stopwatch.

The flow probe was placed snugly (10-20 percent vessel constriction) about a previously dissected segment of dog artery. Either carotid artery or aorta could be frozen and kept for several days before use in these model studies.

In this system it was also possible to study the effects of varying the hematocrit or blood electrolyte content upon flow measurement by the meter. Overaged human blood bank blood was used.

A different model setup was used to test operation of the densitometer-servo-amplifier-computer system in production of dye dilution curves. This setup was a two-compartment model consisting of two syringes mounted in tandem

on a horizontal oscillating shaking table. The first chamber in line was a 10 ml syringe barrel. Dye was injected into the flowing blood just before the first chamber. The next chamber was a 30 ml syringe barrel. Immediately downstream from the larger chamber blood was withdrawn through a side arm by means of a motor-driven withdrawal syringe. A few grams of mercury in each syringe aided in mixing of dye in the chambers as the shaker operated. The foregoing model is similar to that described by Newman et al.

RESULTS

Blood Flow. To some extent this section will be related chronologically. The nature of the work done was dependent upon the arrival of equipment. Ordering was begun early in September 1963. The first major item, the blood flowmeter, arrived in mid-December 1963.

Using temporary recorders for data display, an attempt was made to become familiar with the flowmeter and probes. A model flow system was used in which blood was pumped by a Cole-Parmer pump. The system was abandoned when it became evident that the meter did not respond linearly to changes in flow. The defect was in the model design and a gravity system described above was used subsequently.

With the gravity system it was still not possible to obtain suitable linearity of performance of the flowmeter such as might be expected from the manufacturer's specifications. Moreover, it appeared that the instrument was not stable in the sense that amplifier gain settings drifted and were not reproducible on subsequent runs. In the latter half of January 1964 the flowmeter was returned to the factory for modification.

During March, April and the first week in May, 1964, seven flow model experiments and four dog experiments were run to establish reproducibility of flowmeter readings under various gain settings, conditions of calibration or

with variation in hematocrit. Day-to-day variations were unacceptable and instability of the flow metering system led us to consultation with the manufacturer. It was learned that our flow probes had been sent out without proper shielding on a particular lead wire. They were returned and temporarily replaced by loaned probes.

Dog experiments referred to above involved placing the probe on a carotid artery which was cannulated distal to the probe. In this way blood flow could be metered at the probe site and simultaneously measured by timed collection in a graduate cylinder. The collected blood was heparinized and reinfused into the femoral vein immediately after each flow measurement.

During May and June 1964 ten flow model studies and five dog experiments failed to yield dependable data. The following were reported to the manufacturer of the meter:

1. Non-linear operation of the "probe factor" potentiometer. (The "probe factor" for each individual flow probe is an indication of the gain required for the output meter to show flow directly in ml per min. Thus the required gain is a reciprocal of probe sensitivity. The "probe factor" must be determined for each probe by calibration in a model.)
2. Day-to-day changes in a calculated and calibrated probe factor.
3. Failure to attain proper balance of magnet currents on some occasions.
4. Excessive zero drift on the meter (instrumental zero).
5. By direct measurement meter output varied from 0.85 to 1.0 volt. (Under proper test conditions meter should put out 1.0 volt with imperceptible drift.)
6. The multiplier switch lacks sufficient linearity.

As a result of the above report the flow meter was returned to the company in July for rebuilding. At this writing it has not yet been replaced. (A copy of a letter from Mr. Dennard, President and Chief Engineer of Carolina Medical Electronics is enclosed with this report.)

Cardiac Output. The recorder, servo amplifier and the dye tracer cuvette necessary for cardiac output measurements were received by the end of January, 1964. During periods when flow meter studies could not be pursued, our attention was directed to training personnel and gaining familiarity with cardiac output procedures. At one point, in April, cardiac output studies were interrupted while Gilson Medical Electronics Company modified their dye tracer to provide sufficient voltage to drive the Sanborn cardiac output computer. This was satisfactorily completed.

Five early dog studies in March and April on cardiac output led to the above modification when it was discovered that our cardiac output values were about half the expected values for dogs of comparable size.

May and June were devoted to blood flow work as indicated above and during this period the dye tracer unit was being modified. During July and August dye dilution studies were done on the model, described in the Methods section above, and on dogs.

Forty-six dye curves were produced during various model studies. It was not our purpose here to design an ideal model. Others have devoted considerable time and effort to this (Hamilton, 1928; Newman et al., 1951). We were concerned with steps in technique or procedure which appeared to influence our dye curves in a qualitative way. It was concluded that the model was too imperfect, because of inadequate dye mixing, and it was discontinued once the techniques were learned. The curves, however, were approximating the form to be expected from animal experiments (See Fig. 1).

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CAROLINA MEDICAL ELECTRONICS INC.

3712 REYNOLDA ROAD, WINSTON-SALEM, NORTH CAROLINA 27106

August 24, 1964

Dr. W. D. Collings
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Dear Dr. Collings:

I am writing to let you know the state of your Square-Wave Electromagnetic Flowmeter. We expect that it will be ready for return to you within two weeks.

We regret that your work has been delayed by troubles which have been experienced but we feel that the equipment will function quite satisfactorily upon its return to you.

You may recall that this equipment is a new design which is a rather radical departure from the circuitry used in our very successful earlier models in the 200 series. The basic design is far superior to the earlier models and to competitive equipment. The problems which have arisen are those which were unforseen in the design. As a result of further research, it was found that improved circuitry would further enhance the equipment, make it more stable and eliminate many of the existing problems.

We realize that you have spent several months of your valuable research time and have not yet experienced the results which you had anticipated. We hope that this has not inconvenienced you unduly. We will be pleased to offer whatever assistance we can in working with you and your staff to expediate your work so that additional time will not be consumed in vain.

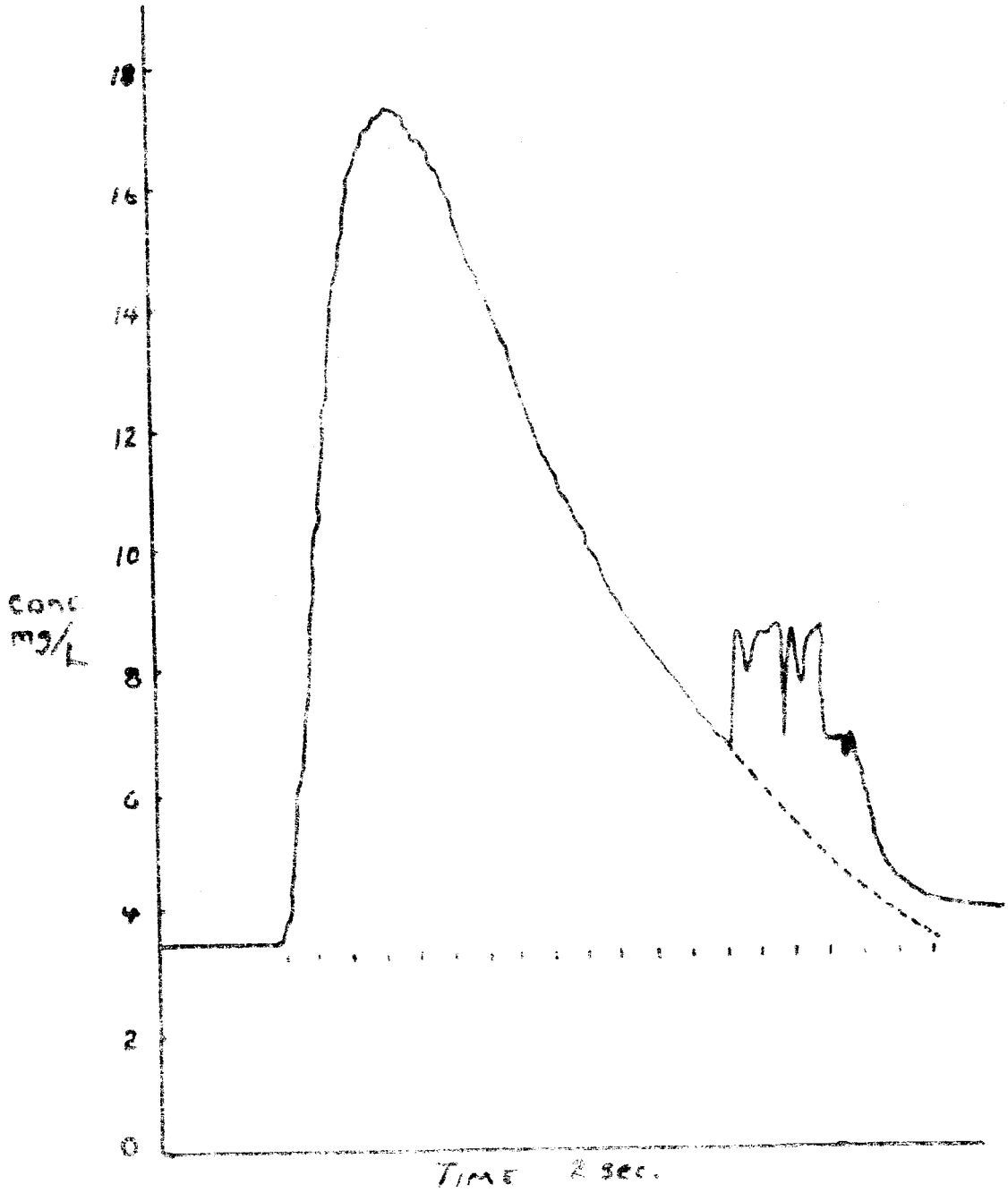
Please do not hesitate to call upon us any time we may be of service.

Very truly yours,

E. J. Dennard, Jr.
President and
Director of Engineering

EJD:jk

Fig. 1. Time-concentration curve from a two-chamber model showing recirculation in cardiac output curves. (Tracing of original recording.)



Twenty-nine dye curves were obtained in studies on five dogs. Four to ten curves were produced for each animal. The purpose of these experiments was to compare cardiac output values computed from dye curves recorded from the servo amplifier and the values calculated from the Sanborn computer reading. It is concluded that the two systems produce satisfactory and corresponding values.

Figure 2 indicates linearity of the computer in response to changing dye concentration in blood. The instrument is stable and the curve shown can be obtained consistently from day to day.

Figures 3 and 4 are tracings of original dye concentration curves for which the servo-gain amplifier was decreased. Reproducibility of curves on successive runs is good. Cardiac output can be determined from these curves by planimetry and the customary equation:

$$\text{Cardiac output (liters/min)} = \frac{I\ 60}{\bar{C}\ t}$$

where I is the quantity of dye injected in milligrams
$\bar{C}$ is the mean concentration of dye during time
and t is the time in seconds for duration of the curve.

Such computed results vary from the computer output values by 7 to 8 percent. Thus far the computer gives consistently higher values. For example the curve in Figure 3 produced a computer value of 2.6 L/min whereas planimetry gave 2.38 L/min. Such agreement is consistently obtainable.

Figure 5 is a reproduction of original records to show replication of curves despite dye accumulation in the animal. Computer values decreased steadily during the series for reasons which are not clear. However, the evidence is that frequent successive estimates of cardiac output can be made in this manner. Gain was twice that used for Figures 3 and 4.

Fig. 2. Plot showing linearity of response of Sanborn cardiac output computer to know dye-blood mixtures.

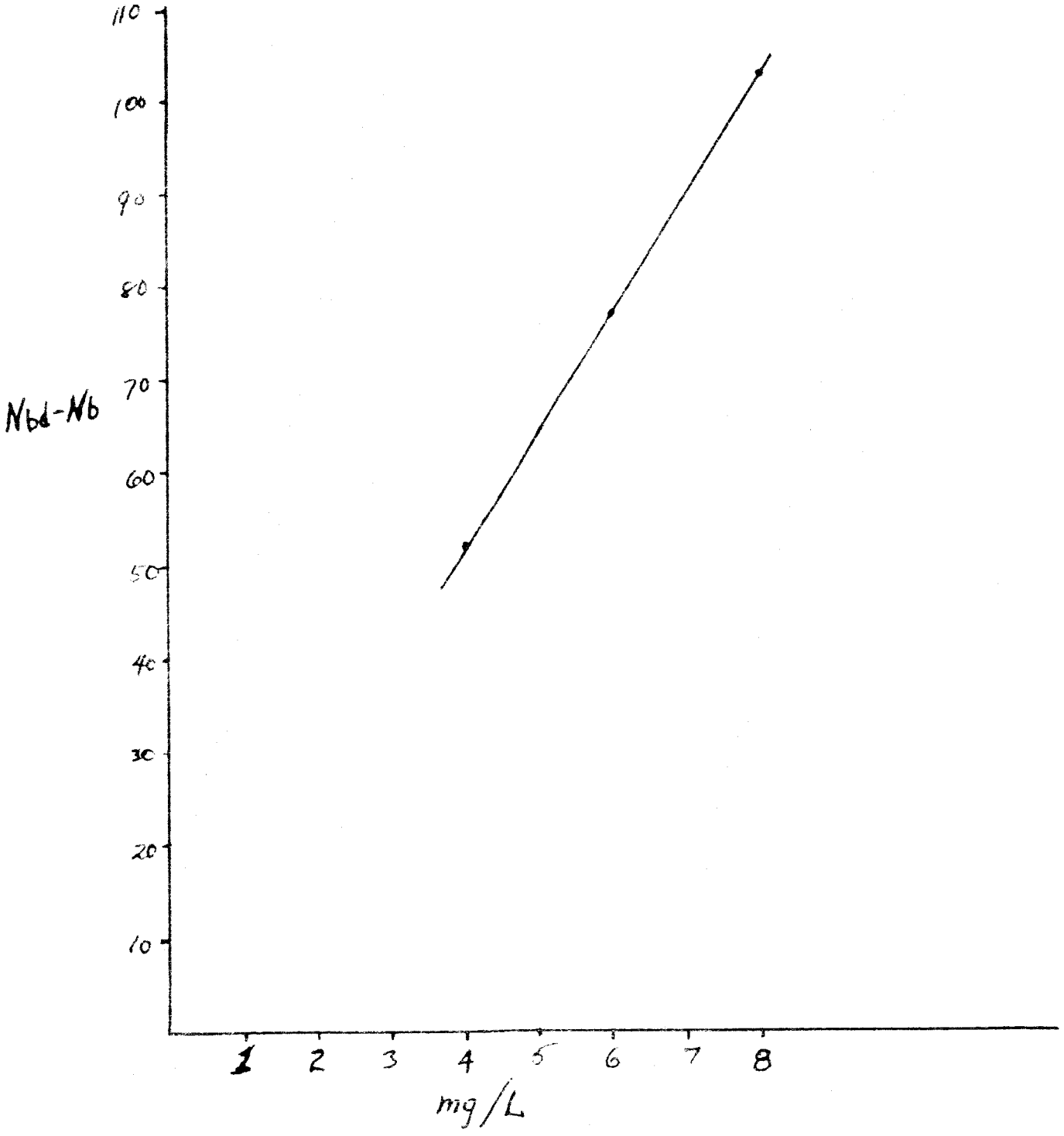


Fig. 3. See Text.

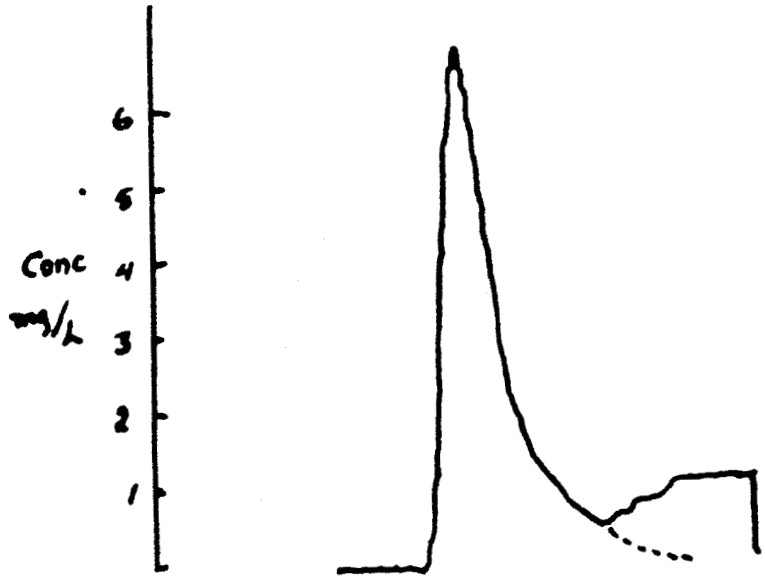


Fig. 4. See Text.

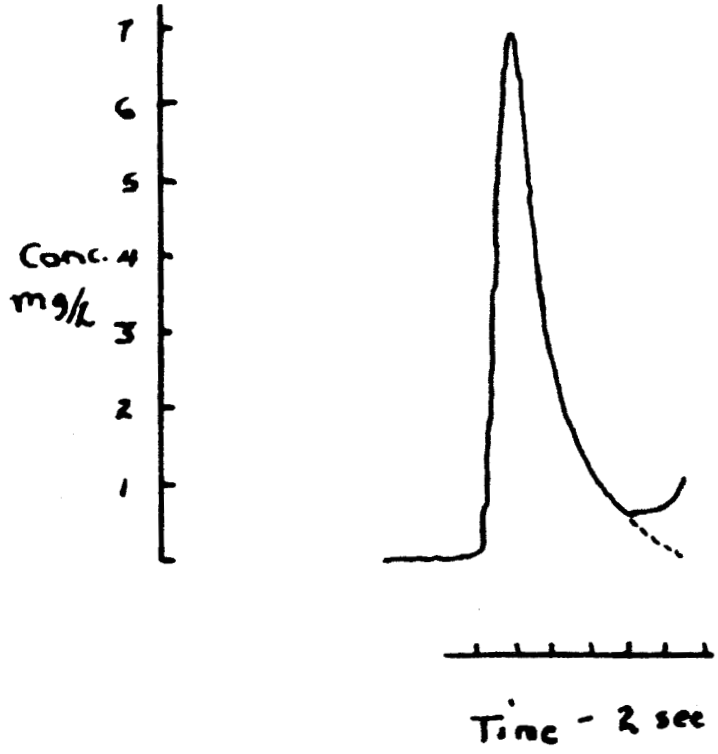


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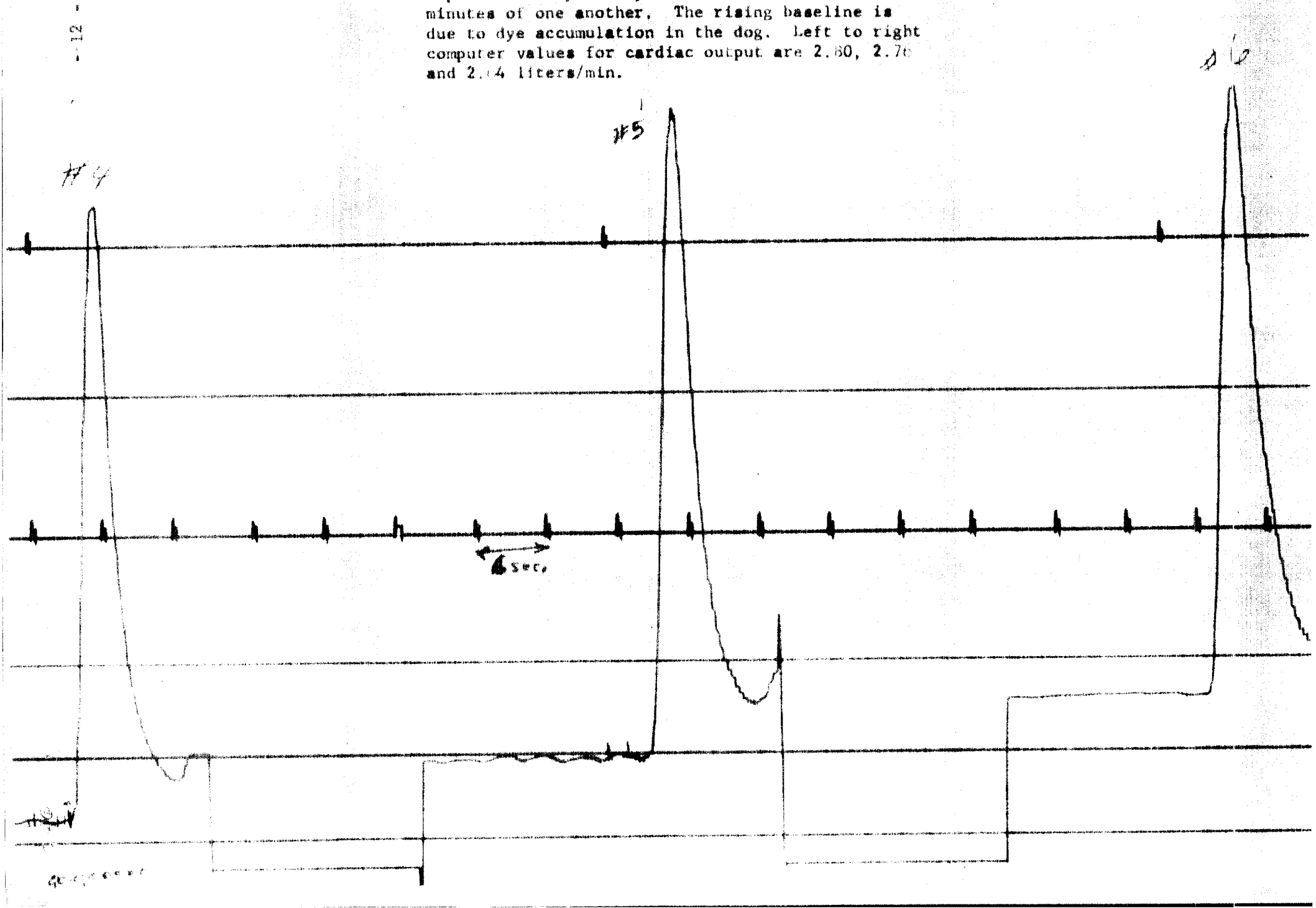
Fig. 5. Three successive dye concentration curves showing reproducibility. They were recorded within a few minutes of one another. The rising baseline is due to dye accumulation in the dog. Left to right computer values for cardiac output are 2.80, 2.76 and 2.74 liters/min.



Two dye curve experiments were accompanied by serial collection of arterial blood samples during the seconds immediately following dye injection. This is the classical Hamilton dye method. However, in this instance colorimetric analysis (Beckman DU spectrophotometer) of the serial samples provided an additional check with the recorder-computer system. As expected the blood samples agreed poorly with the other methods. In a single run the serial samples gave a value 24 percent above the computer. This error might be expected since samples could be collected no oftener than every two seconds and the entire curve had to be based, therefore, on no more than five points.

DISCUSSION

It is clear that no data on blood flow in this project are available at this time. We have never had a properly functioning instrument. As soon as the company makes one available to us, we now have the initial experience to make quick use of the instrument. The company is aware of our predicament and is as cooperative as possible.

Basically, the flowmeter principle is well enough established to be acceptable in this project. Several problems are yet to be faced in its use. First, lengthy chronic implantation of probes, and vessel reaction to them, must be evaluated. Vessel erosion must be prevented and there is reason to believe this can be done by strengthening the vessel wall with woven plastic at the probe implantation site. Flow probes have been installed successfully for periods up to three months (Khouri and Gregg, 1963) and there is no evidence that vessel wall breakdown will always occur.

With respect to cardiac output (whole body blood flow) we are prepared to check the performance of the electromagnetic flowmeter with a probe on the ascending aorta. Despite the short availability of a complete system for less than four months, we have reassuring data which indicate that after flow probe implantation we can evaluate flowmeter function by recorder-computer means with

only minor superficial surgery. By periodic checks on flowmeter performance we will be able to evaluate the extent of drift during prolonged application. The problem of "zero flow" determinations will not be considered where aortic flow studies are being made. It is accepted by some investigators that zero flow is normally seen in the aortic flow pulse during diastole. However, obtaining a flow zero in other arteries is entirely another matter yet to be solved.

Data obtained thus far on this project are inadequate for formal publication. None, therefore, are presented here. Literature citations below are intended only to indicate those authors referred to in the text. There is extensive literature on both blood flow and cardiac output (Guyton, 1963; McDonald, 1960) which can be cited at the time of more formal publication.

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