patterns with (i) other personality factors and (ii) vascular response patterns.

To obtain suitable records for judgment of response pattern, it is necessary to control the circumstances under which the tracing is made. Sensory input and physical activity, for instance, must be held relatively constant.

The write-out demonstrates: (i) whether the subject is asleep, drowsy, or awake; (ii) whether he is active or relaxed; and (iii) which of several patterns of response he demonstrates.

E. Z. Levy
V. H. Thaler
G. E. Ruff
Stress and Fatigue Section, Biophysics Branch, Aero Medical Laboratory, Wright Air Development Center, Wright Patterson Air Force Base, Ohio

Notes

1. The skin resistance meter was designed by Edward Correll of our laboratory in collaboration with Neil Burch.
2. The dry plantar electrodes were developed by Nina K. Morrison of our laboratory.

13 February 1958

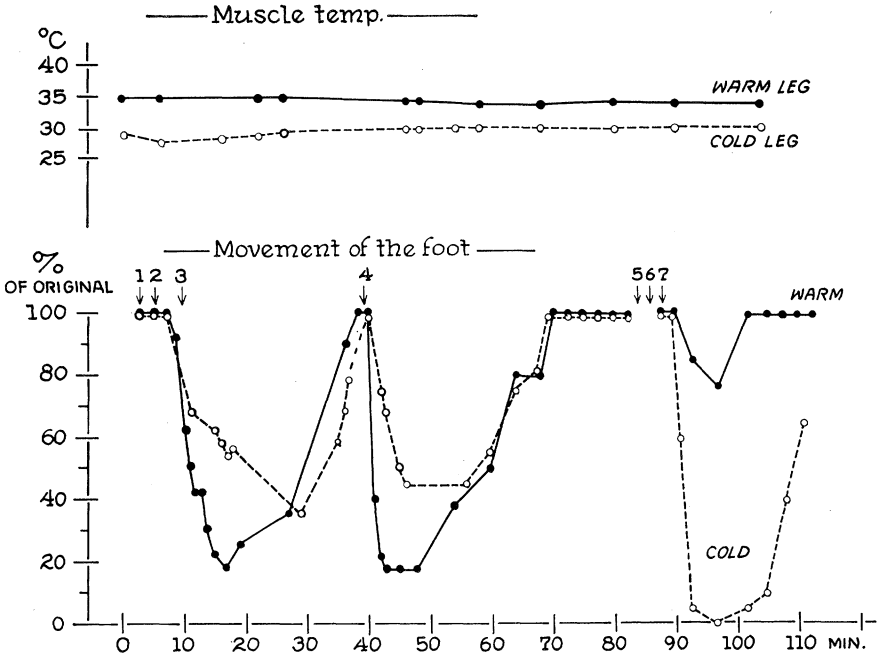

Fig. 2. Simultaneous recording of muscle temperature and the response of the tibialis anterior muscle to indirect stimulation in an anesthetized man. At arrows 1 and 4, 6 mg, and at arrows 2 and 3, 3 mg, of tubocurarine chloride were injected intravenously. At arrows 5, 6, and 7, 2-mg doses of decamethonium diiodide were injected intravenously.

Effects of Lowered Muscle Temperature upon Neuromuscular Blockade in Man

In cats, changes in muscle temperature have a marked influence on the action of neuromuscular blocking drugs (*1*). Experiments both in the intact animal and on isolated tissues have shown that lowering the muscle temperature increases the magnitude and the duration of the action of depolarizing neuromuscular blocking drugs (*2*). This effect is reversed on rewarming. Furthermore, it has been found that the nature of the block is in no way affected by the time duration of the paralysis. On the other hand, when substances, such as tubocurarine, which block by competition with acetylcholine are used, the magnitude of the blockade is reduced by cooling, but the duration of action is only slightly affected. A reduction in the action of tubocurarine by cooling was reported by Holmes *et al.* (*3*) from experiments on the isolated diaphragm of the rat.

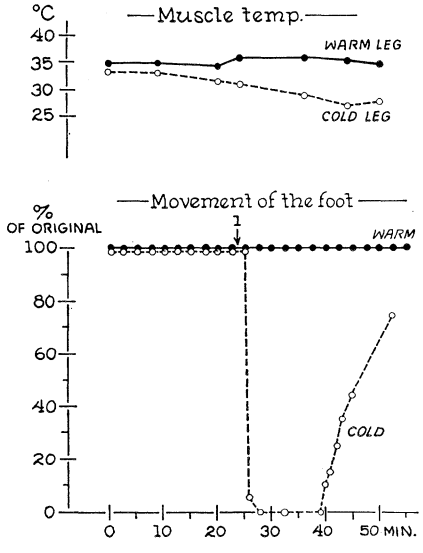

Fig. 1. Simultaneous recording of muscle temperature and the response of the tibialis anterior muscle to indirect stimulation in an anesthetized man. At arrow 1, 1.5 mg of decamethonium diiodide was injected intravenously.

This preliminary report describes analogous results obtained in human beings. Experiments were performed on nine anesthetized patients and two volunteers, in whom a total of 21 blockades were observed. The patients were anesthetized with a short-lasting thiobarbiturate, used in conjunction with nitrous oxide. While the muscle temperature of one leg was lowered by surface cooling, the temperature of the other was maintained at normal level by surface heating. Thermistor needles, inserted into the tibialis anterior muscle of each leg, were used for the recording of muscle temperature. The motor point of the tibialis anterior muscle was stimulated with surface electrodes every 10 seconds, and the movements of the foot thus elicited were recorded on a smoked drum. Three drugs that produce neuromuscular block were studied—decamethonium and suxamethonium, both of which mimic acetylcholine, and tubocurarine, which competes with it. The drugs were administered intravenously, usually as single injections or occasionally in the form of a slow, continuous infusion. A lowering of muscle temperature of 3° to 5°C always increased the magnitude and the duration of a blockade produced by decamethonium and suxamethonium, the duration being affected to a greater extent than the magnitude. Figure 1 illustrates diagrammatically the results obtained in an anesthetized patient. When the muscle temperature of the cooled leg reached 30°C, 1.5 mg of decamethonium was administered intravenously. This dose produced no paralysis in the warm leg, but there was no movement of the cool leg in response to indirect electrical stimulation for 10 minutes. Similar results were obtained with suxamethonium. Thus, the results obtained with depolarizing drugs in human beings are similar to those obtained in cats.

In three of six experiments with tubocurarine, the warm leg was affected more than the cold one; in one, the effect was the same in both legs; and in two, the cold leg was affected slightly more. A possible explanation of this apparent inconsistency lies in the recording system, which was neither sufficiently stable nor sufficiently sensitive to detect small changes. Experiments now in progress in which muscle tension is recorded electrically are providing data in close agreement with those obtained in cats.

Figure 2 illustrates the results obtained in a subject in whom neuromuscular block was produced three times in succession, in the first two instances by tubocurarine and in the third, by decamethonium. The magnitude of the two tubocurarine blocks was reduced by cooling, but that of the decamethonium block

was increased. This demonstrates that the mode of action of decamethonium is fundamentally different from that of tubocurarine and suggests that this mode of action is not altered when tubocurarine has been previously administered.

ELEANOR ZAIMIS
THOMAS H. CANNARD
HENRY L. PRICE
Department of Pharmacology, Royal Free Hospital School of Medicine, University of London, and *Department of Anesthesiology, University of Pennsylvania Schools of Medicine, Philadelphia*

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4. This work was supported, in part, by a grant from the Office of the Surgeon General, U.S. Army (DA-49-007-MD-599).

30 January 1958

Genetic Control of Some Human Serum β-Globulins

The presence, demonstrated by two-dimensional starch-gel electrophoresis (*1*), of an additional β-globulin (D) in the serum of seven individuals (two New York negroes and five Australian aborigines) has been reported by Smithies (*2*). β-Globulin D was present in these sera in approximately the same amounts as β-globulin C. In the several hundred sera previously examined (largely from individuals of European ancestry) β-globulin D was not observed, although β-globulin C was always present.

More work has been carried out with further samples of serum from the five Australian aborigines having both β-globulins C and D, and with sera from other members of their community and race. In all, sera from over 120 aborigines (including several large families) have been examined, and a third β-globulin type has been observed in which β-globulin D is present but β-globulin C is absent. The over-all results suggest that the presence or absence of the β-globulins C and D is under simple genetic control.

The following hypothesis for the genetic control of the β-globulins C and D is completely consistent with the data obtained from the families studied. Two autosomal alleles (β^C and β^D) with no dominance are provisionally postulated. The genotype β^C/β^C leads to the presence of β-globulin C in the serum and to the absence of β-globulin D. The heterozygous combination of genes, β^C/β^D, leads to the presence of both β-globulins C and D in the serum in approximately equal amounts. The third genotype, β^D/β^D, leads to the presence of β-globulin D in the serum and to the absence of β-globulin C. This genetic hypothesis is similar to the three-allele hypothesis proposed by Smithies and Hickman for the control of the five β-globulin types which they have observed in cattle (*3*). It differs from the genetic hypothesis involving five pairs of linked genes referred to by Ashton (*4*) in an independent investigation of the β-globulin variations in cattle.

Figure 1 illustrates diagrammatically the appearance of the two-dimensional starch-gel electrophoresis patterns of the β-globulins in the three phenotypes and gives the postulated genotypes. When sera from the two homozygotes (β^C/β^C and β^D/β^D) are mixed in equal amounts, and the mixture of the two sera is subjected to two-dimensional electrophoresis, the resulting pattern of the serum proteins is indistinguishable from the pattern given by the heterozygote (β^C/β^D), as far as the β-globulins are concerned.

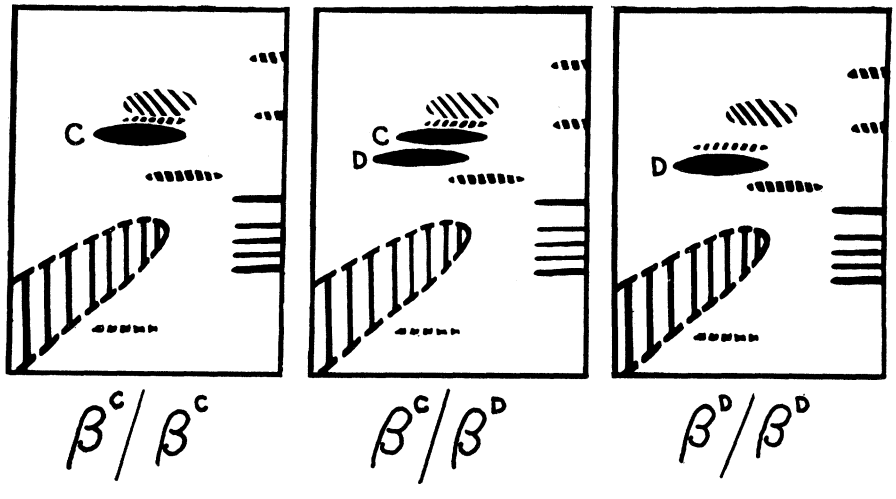

Fig. 1. Diagramatic representation of the stained proteins in the starch gels from two-dimensional electrophoresis (*1*) experiments with the serum β-globulins in the three phenotypes. β-Globulins C and D are labeled in the diagram, and the postulated genotypes are indicated. Each serum sample was first subjected to electrophoresis on filter paper, and that part of the resulting strip over which the β-globulins were distributed was then inserted into a starch gel for the second electrophoresis at right-angles to the first. The β-globulins appear in the central area of each section of the diagram; some of the γ-globulins are to the left of the β-globulins, and some of the α_2-globulins are to the right.

Table 1. Observed distribution of the β-globulin types in the sera of the offspring of those Australian aborigine families in which both parents and at least one child were tested for their β-globulin types, compared with the distribution expected from the genetic hypothesis here considered. The ratios given are (observed/expected).

Matings		Distribution of β-globulin types in offspring		
Observed	No.	βCC	βCD	βDD
βCC × βCC	6	17/17.0	0/0.0	0/0.0
βCC × βCD	6	9/ 9.0	9/9.0	0/0.0
βCC × βDD	1	0/ 0.0	6/6.0	0/0.0

Table 1 summarizes the data obtained from those of the Australian aborigine families studied in which both parents and at least one child were tested for their β-globulin types. The agreement between the observed distribution of β-globulin types in the offspring and the distribution expected from the genetic hypothesis here suggested is excellent.

The haptoglobin types (*5*) of the individuals included in the present study of serum β-globulins were also determined. The genes controlling the haptoglobin types (*6*) and those proposed for the β-globulin types were observed to segregate independently in the one family of those studied in which such independent segregation was theoretically detectable (*7*, *8*).

W. R. HORSFALL
Commonwealth Health Laboratories, Cairns, Queensland, Australia
O. SMITHIES
Connaught Medical Research Laboratories, University of Toronto, Toronto, Canada

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2. O. Smithies, *ibid.* 180, 1482 (1957).
3. O. Smithies and C. G. Hickman, *Genetics*, in press.
4. G. C. Ashton, *Nature* 180, 917 (1957).
5. The haptoglobulins are serum α_2-globulins able to bind hemoglobin; they can be classified in different persons into three types. The haptoglobulin type shown by an individual is determined by his genotype with respect to the alleles Hp^1 and Hp^2.
6. O. Smithies and N. F. Walker, *Nature* 178, 694 (1956).
7. A detailed account of these investigations is in preparation.
8. We gratefully acknowledge the help of Mr. Norman A. Ferris, superintendent of the Mona Mona Mission, in this study, and the technical assistance of Mr. Otto Hiller in the performance of the starch-gel tests.

24 December 1957