appearance of this alteration in Lead II of the E.C.G. for a 3ma current.

Our first thought was that this resulted from a direct effect on the course of polarization of the myocardium. However, further contemplation leads us to believe that this is an electrical impedance effect, in which the electrocardiograph registers, superimposed on the electrocardiogram, alterations in the field distribution which result when the central body impedance changes coincident with ventricular ejection of blood. This is essentially the same effect, generally measured on peripheral body segments, as in electrical impedance plethysmography.

The effect is proportional to the amount of current being passed through the body. With the smaller currents being used in the investigations reported in your *Journal*, one would expect a smaller effect. This effect might possibly cause misinterpretation of clinical electrocardiograms done on subjects who are being electrically polarized. It is also conceivable that, by applying the upper electrode on the base of the neck and underneath clothing, an individual might use the passage of an electrical current through his thorax in an effort at malingering.

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INVOLUTIONAL PSYCHOSIS: SOME NEW AETIOLOGICAL CONSIDERATIONS

DEAR SIR,

Dr. P. R. J. Burch's equation (1) in his paper "Involutional Psychosis: Some New Aetiological Considerations" which appeared in your November, 1964, issue (pp. 825–829) does not follow from his postulates.

Dr. Burch's postulates are simply that, for each individual in the population at risk (*a*) there are a large number, L, of cells at risk and (*b*) the gene somatic mutation rate per cell at risk is m_s. It is required to find the probability that an at risk individual has n or more cells which have had a somatic mutation. This situation is a standard textbook example of a Poisson process (see W. Feller (1950), *An Introduction to Probability Theory and Its Applications*. New York: J. Wiley and Sons, pp. 366), and its analysis may proceed as follows: write $p_r(t)$ for the probability that the individual has accumulated exactly r "somatic mutations generating r genetically identical forbidden clones" at age t then

$$p_r(t+dt) = p_r(t)\,[1-kdt]+p_{r-1}(t)\,kdt$$

$(r \geqslant 0,\ dt \to 0,\ k = Lm_s,\ p_0(0) = 1,\ p_{-1}(t) = 0$ for all t), that is, the probability that there are exactly r forbidden clones at age t+dt equals the sum of (i) the probability that there are exactly r forbidden clones at age t × the probability that no mutation occurs in the age period t to t+dt, and (ii) the probability that there are exactly r−1 forbidden clones at age t × the probability that a mutation occurs in the period t to t+dt.

The above stochastic equation may be written:

$$dp_r(t) / dt = -p_r(t)k+p_{r-1}(t)k$$

which has the well-known solution

$$p_r(t) = e^{-kt}(kt)^r/r!$$

This means that the age specific prevalence (Dr. Burch's equation (1)) at age t is

$$N_t = P_o \sum_{i=n}^{\infty} e^{-kt}(kt)^i/i!$$

This fact was pointed out in the correspondence on Dr. Burch's paper on "Inflammatory Polyarthritis" (1, 2, 3), by Mr. J. Maynard Smith and Mrs. S. Maynard Smith (4, 5), by Drs. R. Augustin and J. A. Spiers (6), and by me (7). Dr. Burch's equation (3) is similarly in error.

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DEAR SIR,

Dr. Pike is a victim of a widespread fallacy. This fallacy involves the failure to distinguish between independent *trials*—described by binomial or Poisson equations—and independent *events*—described by the calculus of independent probabilities. The problem of independent events was correctly analysed by Yule, in the context of evolutionary theory, in 1924 (see also Irwin, 1964).

A good textbook example of "independent trials" is the sequential throwing of a dice. If we throw a dice T successive times ("trials") and if we wish to

calculate the chance of observing exactly, or at least, n "sixes", then binomial equations are relevant. In this kind of experiment we impose a linear sequence on the trials and we may observe successes, say, at the 3rd, 7th, and 15th throws (trials).

When, however, we come to examine a patient of age t years for the presence of 3 independent somatic mutations, we do not take each of his L cells at risk and expose them in turn (L trials) for t years. We actually examine the whole individual. Suppose, however, that by some histological technique we could number these L cells systematically, and suppose we could show that cells numbered 3, 7 and 15 were mutant at t years. From these observations we would be unable to determine the *sequence* in which these three cells became mutant. This contrasts with "independent trial" experiments where the sequence of successes—at the 3rd, 7th and 15th trials—is known. In fact, the three cells could have become mutant in any one of 3! (that is, 6) different sequences and each sequence is equally probable. When kt is small (kt being the probability of any one mutation at t) the probability of each of the 6 distinctive sequences of any three mutations is equal to the probability of finding three successes in the independent trial experiment, that is, $(kt)^3/3!$. It follows, that the probability, at low kt, of observing in a patient *any* one of the 3! equally probable sequences is $(kt)^3$. Provided $L >> n$, the probability of observing any sequence of n mutations at low kt is, by analogy: $(kt)^n$.

This result can be obtained with equal facility from the law of independent probabilities. A set of events is said to be *independent* if the occurrence of any one of them is not influenced by the occurrence of the others. These are the conditions postulated for my somatic mutation model. L is large ($L >> n$) and the occurrence of a mutation in any one cell is not influenced by the occurrence of mutations in other cells. (In the independent trial model, one success follows another in a known *sequence* and this constitutes a *dependent* relationship.) If the probabilities of occurrence of a set of n independent events are: $p_1, p_2 \ldots p_n$, then the probability, P, that all of the set of events will occur, is defined by: $P = p_1 p_2 \ldots p_n$. This is the law of independent probabilities. At low kt, the probability of observing a single mutation is kt, and because mutations are independent, the chance of observing any other similar mutation is also kt. It therefore follows from the above law of independent probabilities that the chance of observing a set of n mutations at low kt is $(kt)^n$—the result obtained above.

When kt is not small it can readily be shown by solving the correct differential equation (Burch, 1964a) that the probability, $P_{\not<n}$, of finding at least n independent mutations is given by:

$$P_{\not<n} = (1-e^{-kt})^n \qquad (1)$$

The probability, P_n, of finding exactly n independent mutations (Yule, 1924; Burch, 1964a; Irwin, 1964) is given by:

$$P_n = e^{-kt}(1-e^{-kt})^n \qquad (2)$$

It would be disconcerting if the age-specific prevalence, or age-specific initiation-rates of "spontaneous" idiopathic diseases in appropriately homogeneous populations never conformed to equation (1) or its relatives. Happily, very good agreement is in fact observed (Burch, 1963, 1964b, 1965; Burch and Rowell, 1965). In the course of many studies I have never found conformity between such data and the logically inapplicable Poisson formalism, except of course when $n = 1$, where no issues of sequence arise, and where the equations for independent trials and independent events coincide.

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BEHAVIOUR THERAPY FOR TRANSVESTISM

Dear Sir,

I was interested to read again reports of the cases of transvestism treated by Barker with aversion therapy (*Brit. J. Psychiat.* March, 1965, 268–276). Though I am in general agreement with much that he says, there are a few points with which I disagree.

I first treated a transvestist with aversion therapy in 1956, and since then my colleagues and I have treated five more. We have used apomorphine, and contrary to what Barker says, it is perfectly possible to utilize the actual process of dressing up in female clothing. It is certainly time-consuming, and the degree of control is obviously much less than with