

Extract from letter to Dr. D. B. Owen, Oct 26, 1934.
ROCKEFELLER FOUNDATION

VII. NEW SCHEME OF RESEARCH IN SEROLOGICAL GENETICS.

Since the early years of the century, it has been known that two agglutinating substances occur spontaneously in human sera, and, from the work of Hirschfeld and others, that these are inherited in a single locus in a system of three, or possibly four, allelomorphs. The system, which appears at present to contain a single common recessive, with absence of dominance among the variant genes A and B bears some resemblance to the factors causing polymorphism in animals known to be polymorphic, such as the grouse locusts and some of the land snails, the genetics of which are now being studied^d at the Galton Laboratory, and, if really analagous, is certainly of evolutionary significance.

More recently, other gene distinctions in man have been shown to be manifested in response to animal sera, especially the so-called immune sera, obtained by injections with human corpuscles. The best of these seem to be M and N found by Landsteiner using rabbits, H found by Schiff, with sheep, while another, or more probably a complex group, is known as P and is manifested in reaction to horse serum.

The list of recent additions to the definitely heritable antigens in man is significant in showing that this list is certainly capable of being much increased in the near future, (i) because only comparatively^e few animals have been tried, and (ii) because with any one animal many distinctions would remain undetected unless both the injections and the agglutination tests were performed with a wide variety of human material.

The second point to note is the simple genetic character of the inheritance in the cases so far investigated, which gives promise that the genetic interpretation of other serological differences would, in general, be far more straightforward than, for example, that of human symptoms or measurements generally is.

The latter conclusion is confirmed by the remarkable investigations of Todd on the immune reactions of poultry. In the stock at his disposal, Todd found that it was easy to produce a serum which could distinguish specifically the corpuscles of one individual bird from those of all others, even though nearly related. His most important finding from the genetical standpoint was that sera which had been exhausted for this reaction for both parents, were without reaction also for all the progeny of the union; a result very simply explicable if the reactions are simply related to the genic constitution, and not otherwise at all intelligible.

The most obvious application of serological genetics lies in the pedigree study of human defects, especially those which are variable and elusive in their manifestation. In this application there are three aims which ought to be pursued: -

(i) Some of the genes causing human anomalies may themselves possess serological reactions, and be thereby capable of unequivocal detection. Persons of genotypes normally anomalous in whom the anomaly is suppressed or obscured could be thus recognised, and a study of inheritance facilitated. Anomalies normally appearing more or less late in life could be detected in childhood. (ii) Some genes which are recessive in their

clinical manifestations and are propagated largely by heterozygous carriers, may yet have serological effects, and so be capable of recognition. (iii) The genes responsible for anomalies, even in the absence of all serological effects specific to them, must certainly be linked with other genes situated in the same chromosomes. As there are only 23 pairs of autosomal chromosomes in man, the prospect, with an increasing number of recognisable serological reactions, of finding at least one, and probably more, linked with those responsible for a given defect or anomaly is not a remote one, provided the means are available for carrying out a systematic research in pedigrees showing anomalies.

In the past the pedigree studies carried out at the Galton Laboratory have consisted principally in the collection of pedigree material, with a special care to clinical symptoms, age of manifestation, etc. As a result, a large number of conditions are, on good evidence, claimed to be inherited, and in many cases, particular families show consistently inheritance of one of the simple kinds, such as autosomal dominants or sex-linked recessives. The study of the material gathered has, however, made several points abundantly clear: - (i) That the same gene can manifest itself in a great variety of clinically distinct conditions, or may be suppressed altogether. (ii) That clinically indistinguishable characters in different families may be inherited in a different way, and must, therefore, be ascribed to the action of different mutant genes. It is undeniable that until pedigree collection is reinforced by a more intensive

study of associated genetic factors, in themselves perhaps harmless or beneficial, these difficulties will continue to harrass the student of medical genetics, and to render all application of his results unreliable.

It should indeed be added that the usefulness of serological methods would not be confined to purely medical investigations. Factors capable of detection in this way may indeed often exert a positively beneficial influence on health, intelligence, artistic appreciation, sensory discrimination, longevity, etc., or at least on factors linked with these. Consequently, any extensive body of data on the heritable genes capable of serological detection, would, as it increases in volume, provide a field for statistical research, from which many results of sociological, rather than purely medical interest might later emerge.

The first step would seem to be to form a small but efficient research unit devoted to the serological study of accessible members of pedigrees of medical interest. A research worker of high scientific capacity and medical training could, at the Galton Laboratory, be given the necessary facilities. He would require the services of a routine assistant, and, later, as the research developed, of a second assistant. The Laboratory already possesses a suitable animal house, but a whole time attendant would be necessary for any extension in the number of animals kept. The Laboratory is in close touch, not only with the University College Hospital, but with the ^{two} ten major research centres on mental defect, under the Darwin Trust (Dr. Penrose) at Colchester, and the Burden Trust (Dr. Fraser Roberts) at

Stoke Park. It is suggested that a programme of five years research should make it possible sufficiently to demonstrate the potentialities of the new method to secure its wider adoption in other centres, which would indeed be greatly facilitated by the existence of any centre whence standardised animals, sera, corpuscles of known reaction, etc., could be obtained. Apparatus and equipment would probably not constitute a large item, initially, little more than the cages and stocks of animals and adequate equipment for cold storage of material.

VIII. COST OF NEW SCHEME OF RESEARCH IN SEROLOGICAL GENETICS.

If the Rockefeller Foundation were prepared to support the scheme, it is suggested that for the "demonstration" period of five years, a Rockefeller Fellowship should be made tenable at University College, and that a grant should be made in aid of his expenses of research. It would be understood that neither the Rockefeller Foundation nor University College would be committed to continuing the experiment beyond the demonstration period. The Rockefeller Fellow, and his assistants would be appointed on that understanding; they would not be placed on the established staff of the College. The cost during the demonstration period would then be: -

(cont. on page 6)

Section VIII (contd.)

(8)

	<u>1935-36</u>	<u>1936-37</u>	<u>1937-38</u>	<u>1938-39</u>	<u>1939-1940</u>
Rockefeller Fellow (£650 by £25 to £750)	£650	£675	£700	£725	£750
Contribution to Superannuation Scheme	65	68	70	73	75
Expenses of Research:					
(1) Assistant at £200 by £25 to £300	200	225	250	275	300
(2) Assistant at £200 by £25 to £250	+	-	200	225	250
(3) Superannuation of Assistants	20	23	45	50	55
(4) Boy for Animal House at £1 per week	52	52	52 ⁿ	52	52
(5) National Health & Unemployment Insurance	12	12	12	12	12
(6) Material	80	80	80	80	80
(7) Initial Equipment	200	-	-	-	-
	<u>£1,279</u>	<u>£1,135</u>	<u>£1,409</u>	<u>£1,492</u>	<u>£1,574</u>

It will be noted that provision has been made for superannuation. Members of the staff of the Universities of Great Britain are admitted to a contributory scheme known as the Federal Superannuation Scheme, the University contributing 10% and the member 5% of his salary towards the purchase of an Endowment or Deferred Annuity Policy. Provision has been made for the University contribution to the Federal Superannuation Scheme in respect of the Fellow and his Assistants, as it may well be desirable to employ persons who are either already on the staff of a University or will go on to such a staff after holding a post here.